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LIPID NEPHROSIS

OBSERVATIONS OVER A PERIOD OF TWENTY YEARS

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AND
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NEW YORK
AND
SAMUEL B. WEINER, M.D.
FOREST HILLS, N. Y.

The term lipid nephrosis was first used by Müller [1] to distinguish the purely degenerative type of renal lesion from the inflammatory type. After many evolutions it has come to designate a malady characterized by an insidious onset, generalized recurrent edema, normal blood pressure, massive albuminuria, a normal blood urea content, a high serum lipid level and a low value for total serum protein and for albumin (Volhard and Fahr [2] and others). Epstein [3] suggested that the cause of lipid nephrosis is extrarenal and that the symptoms are caused by a disturbance of protein metabolism. Schick [4] and Addis [5] suggested that the source of this protein disturbance may be in the liver.

If one accepts lipid nephrosis as a distinct clinical entity, it is rather infrequent. In over twenty years in the pediatric service at the Mount Sinai Hospital we have made such a diagnosis for only 40 children. In that same period we [6] observed over 400 children with typical symptoms of acute or chronic glomerular nephritis. It was only when we realized clinically that the course was not the usual one of a glomerular nephritis

From the Pediatric Department and the Laboratories of Mount Sinai Hospital.

Read before the Section on Pediatrics at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1942.

1. Müller, F.: Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch. **9**:64, 1905.

2. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit; Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

3. Epstein, A.: The Nature and Treatment of Chronic Parenchymatous Nephritis (Nephrosis), J. A. M. A. **69**:444 (Aug. 11) 1917.

4. Schick, B.: Personal communication to the author.

5. Addis, T.: Personal communication to the author.

6. Schwarz, H.; Kohn, J. L., and Weiner, S. B.: The Prognosis of Nephritis and Nephrosis in Childhood, New York State J. Med. **40**:409 (March 15) 1940.

that we designated the condition, often with hesitation, as a nephrosis. On long follow-up, however, many patients subsequently manifested some of the symptoms of a glomerular nephritis.

We know that 22 of the 40 patients have died (table 1). In our follow-up clinic the surving children have been seen regularly, at least three times during the year. A complete physical examination and urinalysis have been made each time. Chemical examinations of the blood have been made from time to time.

We have followed 8 of these patients from seven to twenty years. All but 1 have been seen in the last few weeks. Six of these are 15 years of age or older (table 2).

TABLE 1.—*Total Patients with Lipid Nephrosis*

Total patients seen	40
Known dead	22
Living when last seen	18
Last seen in 1942	8
Necropsies	12

TABLE 2.—*Living Patients*

Number of Years Followed	Number of Patients	Last Seen	Present Age Year
20	1	1942	22
17	1	1942	19
16	1	1942	23
14	1	1942	16
13	1	1942	17
9	1	1940	15
8	1	1942	10
7	1	1942	10
3	1	1932	
2	2	1924-1925	
1 and less	7	1924-1938	

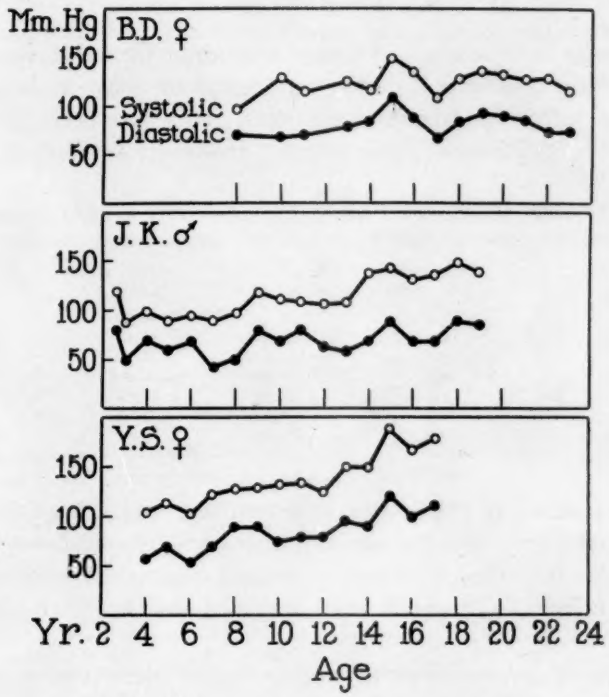
We shall be unable to give all our observations, but will confine ourselves to three phases: (1) the prolonged observation of these patients during and beyond their puberty; (2) the effect of certain acute infections, especially measles, on the course of this condition, and (3) some observations on necropsy of some of our patients.

I. Prolonged Observations.—Some years ago we [7] published a report on fifteen years' observation of our patients with nephrosis. We stated that there had been an apparent cure in some children. However, on further observation a distinct rise in blood pressure during early puberty was noted in several of these children. The children have otherwise

7. Schwarz, H., and Kohn, J. L.: Lipoid Nephrosis: A Clinical and Pathologic Study Based on Fifteen Years' Observation with Special Reference to Prognosis, Am. J. Dis. Child. **49**:579 (March) 1935.

remained clinically well. Blackman [8] stated that no prolonged observations of blood pressure have been made on children who are believed to have had lipid nephrosis. In our patients this rise in blood pressure was higher, both systolic and diastolic, than the rise of blood pressure sometimes noted in normal puberty. During normal puberty the blood pressure may rise to 135 mm. systolic but the diastolic pressure stays between 65 and 80 mm.

The blood pressure was increased at some time in all 8 patients who were observed over a long period. In 4 of these, the blood pressure has



Course of blood pressure in 3 children first seen with clinical lipid nephrosis.

returned to normal and remained so for several years. In 1 patient, observed for thirteen years, now 17 years old, the blood pressure at present is 190 mm. systolic and 120 mm. diastolic. Another, observed seventeen years, now aged 19 years, has a blood pressure of 150 mm. systolic and 90 mm. diastolic. One girl, who is now 23 years old, had a persistent blood pressure of 150 mm. systolic and 90 mm. diastolic. Twice during early pregnancy she has had miscarriages. Within the last few months the blood pressure has returned to normal.

8. Blackman, S. S., Jr.: On the Pathogenesis of Lipoid Nephrosis and Progressive Glomerulonephritis, Bull. Johns Hopkins Hosp. **57**:70 (Aug.) 1935.

We have made Addis urinary sediment counts in recent weeks for 7 of the children followed over seven years. In 4 the red blood cell content was definitely high; in all but 1 of the others there was a slight increase above the normal. The limit of normal for red blood cells in the urinary sediment of children as given by Lyttle [9] is 600,000 in twelve hours and of adults (according to Goldring [10]) 500,000. The normal count for casts is from 15,000 for children to 5,000 for adults. The urinary sediment showed the largest number of red cells in the children observed over the longest periods, that is, twenty, seventeen and sixteen years respectively. In 2 children there was an increase in urinary casts (table 3).

II. Response to Infection.—We wish to describe the beneficial results on the nephrotic syndrome if during an edematous phase such patients get an acute infection, especially measles. This has been noted by Schick,[4] Tezner and Stross [11] and others. However, an acute infection

TABLE 3.—*Addis Counts on Patients Observed Over a Long Period*

Patient		Urine per 12 Hr., Cc.	Red Cells	Casts	Years Followed
Y. S.	.....	125	830,000	80,000	13
B. D.	.....	335	3,300,000	None	16
J. G.	.....	220	None	None	8
J. K.	.....	220	18,750,000	150,000	17
R. P.	.....	410	1,350,000	None	14
N. D.	.....	220	750,000	None	8
I. S.	.....	235	1,700,000	None	20

may be detrimental, as there often is a resultant sepsis, pneumonia or peritonitis. The prognosis for patients with such complications may be improved now that they are usually treated with chemotherapy and intravenous injections of amino acids, as suggested by Farr and Mac Fayden.[12]

In 3 children a remarkable temporary improvement was seen after an acute infection. In 1 of them the improvement followed an acute tonsillitis, and in the other 2 it followed measles. There was a diuresis with loss of edema. The albuminuria, as shown by the usual clinical tests, was considerably reduced or disappeared for several months. In 1 child the edema recurred after three months, and the child subsequently

9. Lyttle, J. D.: Addis Sediment Count in Normal Children, J. Clin. Investigation **12**:87 (Jan.) 1932.

10. Goldring, W.: Observations on the Clinical Application of the Urine Sediment Count (Addis), Am. J. M. Sc. **182**:105 (July) 1931.

11. Tezner, D., and Stross, J.: Der Einfluss der Masern und des Nirvanol Exanthems und der Verlauf der genuinen Nephrose, Monatschr. f. Kinderh. **49**:1 (Jan.) 1932.

12. Farr, L. E., and MacFayden, D. A.: Hypoaminoacidemia in Children with Nephrotic Crises, Am. J. Dis. Child. **59**:782 (April) 1940.

died of peritonitis two years later. In the second child, now 10 years of age, the edema recurred for a time. He is at present clinically well. The third, now 19 years old, has no subjective symptoms but has an intensive increase in the number of red blood cells and casts, determined by the Addis count.

We do not recommend that a child in the edematous state should be directly exposed to measles or other acute infections. On the contrary, it has been our experience that patients who have the classic symptoms

TABLE 4.—*Beneficial Effect of Acute Infection (Measles) on Course of Edema and Urinary Albumin in Patient N. D.*

Age, Years		Edema	Urinary Albumin	Serum Protein, Mg. per 100 Cc.
2		++	++++	4.2
2½		+	+++	4.4
	Measles			
3		0	+	6.4
3½		slight	0	5.8
4		+	+++	
5		slight	++	4.0
6		0	0	5.6
7		0	0	
8		0	trace	
9		0	0	
10		0	0	

TABLE 5.—*Cases with Fatal Termination*

Number of Years Followed		Number of Cases	Necropsies
3½		1	1
3		1	1
2½		1	1
1½		2	2
1 or less		17	7

of chronic glomerular nephritis with edema show no improvement after acute infections.

III. Postmortem Observations.—As noted, there were twelve postmortem examinations. The children usually died from a secondary infection which started from one month to three and a half years after the onset of the original symptoms. We could not predict from the clinical course the extent or intensity of the glomerular changes. At some time during the illness of most of these children we found a moderate increase in blood pressure, slight nitrogen retention, occasional casts and a rare red blood cell in the urine.

The histologic changes observed in the kidneys varied in accordance with the time of onset of the first clinical symptoms: (1) In 7 children

on whom a necropsy was made one year or less after the onset of symptoms the glomeruli showed either no pathologic changes or slight congestion of the capillary loops. (2) In the 5 children who died one year after the onset of the symptoms the glomerular changes could be divided into two groups: (*a*) glomerular nephritis with some interstitial scarring and obliteration of some glomeruli. This was not as extensive as that seen in a typical progressive glomerular nephritis. This was found in 2 children. (*b*) In the other 3 children there was a definite thickening of some of the glomerular capsules. An occasional tuft showed evidence of swelling and was adherent to the capsule. In all the necropsies the convoluted tubules of the kidneys showed swelling of the lining cells with vacuolation. These changes in both the glomeruli and the tubules have been fully described by Wolbach and Blackfan [13] and others.

One child in the last group was first seen by us with a typical clinical picture of acute glomerular nephritis, including gross hematuria. This child was discharged much improved after six weeks. She returned after three months with a typical nephrotic syndrome. The patient died of peritonitis nine months after the second admission to the hospital. We suspected before necropsy that the child had a glomerular nephritis accompanied by a nephrotic syndrome. To our surprise, the necropsy showed only an occasional glomerulus with a thickened capsule and an occasional swelling of the tuft adherent to the capsule. This was the first time that a patient while under our observation had at the onset all the symptoms of an acute glomerular nephritis which was later followed by a nephrotic syndrome and did not at necropsy show the lesions of a progressive glomerular nephritis.

COMMENT

We prefer to limit our remarks about this disease to its manifestations in children only. If lipid nephrosis is an entity, it should be present in its purest form in children. In adults there may often be a previous complicating factor. We have had the advantage of seeing these children soon after the symptoms were first noticed. With this long period of observation we should be able to trace the natural history of this syndrome.

We have pointed out that 8 patients had been observed from seven to twenty years. Four of the older group showed in later phases hypertension, occasional albuminuria and increased Addis counts. The others have, with 1 exception, at present an increased Addis count and no hypertension. We think we have the right to say that these patients had a glomerular nephritis from the onset. The clinical expression represented in the nephrotic syndrome would then be a phase in the life cycle of the disease.

13. Wolbach, S. B., and Blackfan, D.: Clinical and Pathological Studies on So-Called Tubular Nephritis (Nephrosis), Am. J. M. Sc. **180**:453 (Oct.) 1930.

An important observation was the improvement of some patients—perhaps only temporarily—after an acute infection, such as measles. Why did the kidney become less permeable to albumin, and what induced the diuresis? We cannot give a satisfactory explanation of the mechanism of this effect. Such improvement is not noted in chronic glomerular nephritis.

In most of our necropsy material the histologic picture of the glomeruli is different from that seen in chronic glomerular nephritis. We reported on a patient who was first seen by us with a typical clinical picture of acute glomerular nephritis with gross hematuria. She manifested within the next year typical symptoms of lipid nephrosis. The patient died of peritonitis. The necropsy showed meager glomerular changes.

Moschcowitz [14] stated that the lack of the usual lesions of glomerular nephritis does not necessarily imply that such lesions have not existed. We are well informed of the evolution of the glomerular changes in the clinically progressive chronic glomerular nephritis, whether associated with a nephrotic component or otherwise, but are unacquainted with the conditions of the glomeruli in the clinically healed patients.

Observing each patient over long periods, we believe that the clinical entity of true lipid nephrosis is rare. If one may judge from the later course of the disease, there is no need to seek an extrarenal cause for the classic picture.

SUMMARY

We have made a diagnosis of lipid nephrosis for 40 children over a period of twenty years. Twenty-two of the patients we know to have died.

Eight patients were followed from seven to twenty years. Four of these children now have hypertension and increased urinary sediment counts (Addis). Two others have increased urinary sediment counts only.

The beneficial effect of an acute infection during the edematous phase is discussed.

The histologic observations in 12 necropsies is discussed. One could not predict from the clinical course the pathologic changes in the kidneys.

We conclude, therefore, that most children with the classic clinical picture of lipid nephrosis have a glomerular involvement but perhaps in a different form from that seen in chronic or subacute glomerular nephritis.

110 East Ninetieth Street.

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14. Moschcowitz, E.: The Validity of Nephrosis as a Nosological Concept, J. Mt. Sinai Hosp. **8**:878 (Jan.-Feb.) 1942.

ABSTRACT OF DISCUSSION

DR. LEE E. FARR, Wilmington, Del.: As Drs. Schwarz, Kohn and Weiner pointed out, it is only after careful study and observation that one can be justified in making a tentative diagnosis of nephrosis. Because specific positive diagnostic criteria are lacking, a final diagnosis of nephrosis can be made only at the autopsy table. Nevertheless, careful clinical studies make possible the separation from the larger group of patients with the nephrotic syndrome of a group of patients in whom the required pathologic changes predominate. Patients in this group are rare, and I believe it is likely that because of the interest of the authors in the nephrotic syndrome this group comprises a somewhat larger percentage of the patients with Bright's disease whom Drs. Schwarz, Kohn and Weiner have studied than might normally be encountered.

The mortality is high, in the present series 55 per cent. I have had an opportunity to study for over seven years 60 children with nephrotic manifestations who were selected because their history and physical examination suggested pure nephrosis. At the end of a six year period, on the basis of observations made clinically and in the laboratory, 36 of the children were separated into a group the data on whom seemed compatible with a diagnosis of nephrosis, the remaining 24 being classed as having chronic glomerulonephritis. The mortality in this group of 36 was 16 patients, or 44 per cent, and will probably reach at least 50 per cent. In my series 10 of the 36, or about 28 per cent, recovered completely. As yet there has been no opportunity to follow any of these recovered children through puberty, since they are just reaching that age. If the occurrence of hypertension at the time of puberty, which Drs. Schwarz, Kohn and Weiner reported in their recovered group, can be further substantiated and shown to be of significance for the patient's future, it is an important observation and may change our beliefs regarding recovery from this disease.

Absence of hematuria is always given as one of the primary diagnostic requirements for nephrosis. Yet it is the common experience of workers in this field that some patients who have abnormal Addis counts do not exhibit phenomena usual in classic chronic glomerulonephritis. Of my series of 36 children, classified as I previously mentioned, 19 showed an increased number of red cells in the urine by one or more Addis counts. Observations on this group aggregate 45 patient years, and 134 Addis counts were done. Two patients died before Addis counts were made. In 15 patients, on whom the observations aggregate 44 patient years and for whom 123 Addis counts were done, on no occasion were red cells found in excess of the number accepted as the upper limit of normal for children. Despite these differences in Addis counts, this group seems to be a homogenous unit, and this impression has been strengthened by necropsy studies on 15 patients. It would appear that Addis counts in themselves are not a sufficiently accurate reflection of histologic changes occurring in the kidneys to warrant their being used as the sole criterion for differential diagnosis. This is emphasized by the patient observed by Drs. Schwarz, Kohn and Weiner who at one time had an acute nephritis on the basis of urinary observations but in whom a nephrotic syndrome developed and who at necropsy had no glomerular changes.

In regard to the effect of infections on the course of this disease in children, I am much more pessimistic than Drs. Schwarz, Kohn and Weiner. I have never seen a patient make a dramatic recovery after an infection, including measles. In a few instances I have seen loss of edema and clinical improvement in the wake of an infection but never recovery. I believe infection is always a crisis for these children and should be prevented if possible.

The diagnosis of nephrosis at present depends on histologic study of the kidneys. Here, too, the criteria rest on a negative rather than a positive basis, i. e. absence of change in glomerular structures. This is unsatisfactory. The histologic picture of the glomeruli in these patients is different from that seen in chronic glomerulonephritis. In many instances the diagnosis depends on an interpretation of what constitutes thickening of the basement membrane. If nephrosis is a stage in nephritis, no one has yet clearly shown why in one instance after the disease has been active for years the only glomerular lesion may be degenerative whereas in another instance fibroblastic proliferative changes appear early and progress steadily to destruction of the nephron. It seems entirely possible that final diagnostic criteria for nephrosis may rest on a demonstration of specific changes in function rather than in renal histology.

The resolution of the question of whether nephrosis is a disease entity will, I believe, eventually be solved by extensive longitudinal studies of the type which has just been reported. I wish to compliment Drs. Schwarz, Kohn and Weiner on their report. It has entailed a tremendous amount of work, and all of us now have a clearer conception of the natural history of the nephrotic syndrome than we had before.

Dr. Jerome L. Kohn, New York: I stated that the beneficial effect of an acute infection on the nephrotic syndrome was only temporary. Since this paper was completed we have observed 4 additional patients in whom the albuminuria and the edema disappeared for several months following acute infections. We agree wtih Dr. Farr that Addis counts should not be the only criterion of an active nephritis. Dr. Caldwell stated that he obtained improvement in 2 nephrotic patients by giving large doses of vitamin A. We recently gave large doses of vitamin A, under Dr. Caldwell's direction, to 2 patients. Neither patient improved. We intend to use this form of treatment for additional patients before evaluating its effectiveness.

EXCRETION OF 17-KETO STEROIDS BY NORMAL AND BY ABNORMAL CHILDREN

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INTRODUCTION

The present article extends previous observations on the total output of neutral urinary 17-keto steroids of children.[1] The establishment of normal standards of excretion of these substances by normal children of different ages and sexes, as determined by the analytic methods now available,[2] is essential for the evaluation of the excretion of these substances in the urine of abnormal children. Section I of this paper presents such normal figures as standards of comparison. Observations on children with physiologic and pathologic variations in growth and development are reported in sections II and III.

METHODS AND MATERIAL

Accurately timed overnight or twenty-four hour specimens of urine were collected, and approximately 5 cc. of hydrochloric acid was added as preservative.

This work was supported by a grant from the Commonwealth Fund, New York.

From the Department of Pediatrics, Harvard Medical School, the Children's Medical Service, Massachusetts General Hospital, and the Children's and Infants' Hospitals.

1. (*a*) Talbot, N. B.; Butler, A. M., and MacLachlan, E. A.: Alpha and Beta Ketosteroids (Androgens): Preliminary Observations on Their Normal Excretion and the Clinical Usefulness of Their Assay in Differential Diagnosis, New England J. Med. **223**:369, 1940. (*b*) Talbot, N. B.; Butler, A. M., and Berman, R. A.: Adrenal Cortical Virilism: Diagnosis, Course and Treatment, J. Clin. Investigation **21**:559, 1942.

2. (*a*) Talbot, N. B.; Berman, R. A.; MacLachlan, E. A., and Wolfe, J. K.: The Colorimetric Determination of Neutral Steroids (Hormones) in a Twenty-Four Hour Sample of Urine, J. Clin. Endocrinol. **1**:668, 1941. (*b*) Talbot, N. B.; Berman, R. A., and MacLachlan, E. A.: Elimination of Errors in the Colorimetric Assay of Neutral Urinary 17-Ketosteroids by Means of a Color Correction Equation, J. Biol. Chem. **143**:211, 1942.

The urine was stored at ice box temperature until it was assayed. After hydrolysis, extraction and partial purification, the total content of neutral 17-keto steroids of each sample was determined by the absolute alcoholic metadinitrobenzene–potassium hydroxide color reaction as described elsewhere.[2a] A color correction equation [2b] was employed to reduce the error of overestimation due to chromogens not 17-keto steroids.[3]

A total of 201 determinations of the urinary excretion of 17-keto steroids per twenty-four hours were carried out on 104 normal subjects between the ages of a few hours and 47 years.[4] Of these, 31 were made on 31 girls ranging in age from 4 to 18 years; 69 were made on 69 boys ranging in age from a few hours to 18 years; 89 were made on 4 normal women, and 12 were made on 3 normal men. A total of 71 additional determinations were made on 64 children with various diseases (tables 2 to 6).

RESULTS

I. NORMAL SUBJECTS

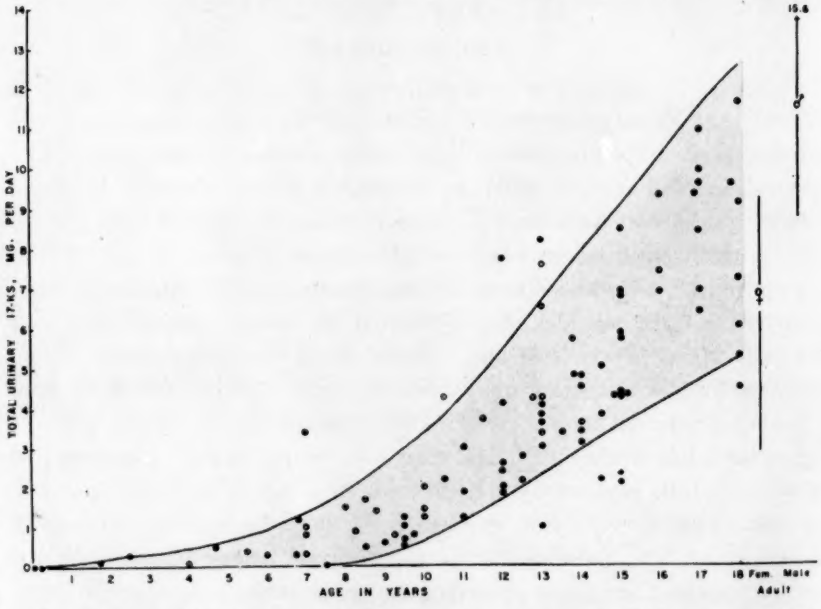
1. Effect of Age.—The total milligrams of neutral 17-keto steroids excreted per twenty-four hours by normal persons is plotted as the ordinate against the chronologic age as the abscissa in the chart. The left portion of the chart gives the individual values obtained for boys (black circles) and girls (white circles) under 18 years of age. There was no significant difference between the output of boys and girls within this age limit. The shaded area between the two curves running upward from left to right includes 90 per cent of the values obtained for boys and girls up to 18 years of age. Thus. the shaded area should define the approximate normal range of values for the excretion of 17-keto steroids at different ages. At the right side of the figure are average values for adult women (♀) and men (♂) respectively. The range in values for adults is given by vertical lines running through the ♀ and ♂ symbols respectively. For convenience in appraising the output of 17-keto steroids by patients, the average normal values described by the data in the chart are listed according to age in table 1.

The average values of table 1 show that from birth to approximately 8 years of age the values for urinary excretion of 17-keto steroids were low. The values of the present report are lower than those reported

3. There is an error on page 211 of that paper. Read E_b/E_g for E_g/E_b in the second and third lines from the bottom of the page.

4. Two private day schools (Rivers County Day School and Winsor School) located in greater Boston made the collections of urine from 45 of the boys and 7 of the girls. Dr. G. Hoeffel made arrangements for urine collections from 6 "hospital normal" children at the New England Peabody Home. He also collected the urine of several of the children with hypothyroidism. The patients with mongolism were studied through permission of Drs. F. Perkins and F. B. Talbot. The remainder were "hospital normal" children and patients at the Children's Hospital, and the Children's Medical Service of the Massachusetts General Hospital.

previously by Oesting and Webster,[5a] Nathanson, Towne and Aub [5b] and ourselves [1a] because of the modifications in the procedure for assay of 17-keto steroids which have been introduced to reduce the errors of overestimation due to interfering chromogens.[2b] During the period from 8 to 18 years, the average output rose from less than 1 mg. to approximately 9 mg. per day. The curves of the chart, which depict the normal ranges in output of 17-keto steroids, also show that whereas for children under 11 years of age the low upper limit of normal excretion permits the easy detection of an abnormally high excretion, the negligible lower limit of normal excretion renders detection of hypoexcretion impossible. The lower curve indicates, however, that children should be excreting at



Excretion of 17-keto steroids by normal persons. The black dots indicate values for boys; the circles, for girls. (See text for further explanation of chart.)

least 1 mg. a day after they have passed their twelfth birthday. The points which fall outside of the shaded area of the chart presumably represent extreme normal variations. Adult women had values which corresponded closely to those obtained for children 17 to 18 years old (average 7 mg.). Men excreted more 17-keto steroids (average 11 mg.) than women or older children.

2. Day by Day Variation.—The day by day variation in the excretion of 17-keto steroids by a single subject was investigated by daily measure-

5. (*a*) Oesting, R. B., and Webster, B.: The Sex Hormone Excretion of Children, Endocrinology **22**:307, 1938. (*b*) Nathanson, I. T.; Towne, L. E., and Aub, J. C.: Normal Excretion of Sex Hormones in Childhood, ibid. **28**:851, 1941.

ments obtained on 3 of the adult subjects. An analysis of eighty assays on 2 normally menstruating women showed that two thirds of the values fell within ± 15 and ± 12 per cent of the average value for each subject, respectively. In no instance did any value obtained for 1 subject deviate from her average value by more than ± 30 per cent. Approximately similar results were obtained in assays for a normal man and in assays for 2 children.

These observations on the day by day variation in the amounts of 17-keto steroids excreted confirm the opinion of Bachman, Leekley and Winter [6] and Fraser, Forbes, Albright, Sulkowitch and Reifenstein [7] that a single determination of the output of 17-keto steroids of a person under normal circumstances is reasonably representative of his output.

3. Comment.—Nathanson and his co-workers have pointed out that the rise of 17-keto steroids in the urine during adolescence correlates

TABLE 1.—*Average Output of 17-Keto Steroid per Day by Normal Persons of Various Ages*

Age, Years	17-Keto Steroid Output, Mg.	Age, Years	17-Keto Steroid Output, Mg.
3	0.15	12	3.4
4	0.3	13	4.3
5	0.4	14	5.3
6	0.5	15	6.3
7	0.65	16	7.2
8	0.95	17	8.1
9	1.4	Adult women	6.8
10	1.9	Adult men	11.0
11	2.6		

with the increase in size of genital structures and of muscle mass.[8] Because the adrenal cortex and the testes are believed to be the normal sources of urinary 17-keto steroids,[9] the finding that boys did not excrete significantly greater amounts of these substances than girls suggests that the adrenal cortex is the chief site of origin of the 17-keto steroids

6. Bachman, C.; Leekley, D., and Winter, B.: Day and Night Excretion of Pregnandiol Glucuronidate and Neutral 17-Ketosteroids in Pregnancy, J. Clin. Endocrinol. **1**:142, 1941.

7. Fraser, R. W.; Forbes, A. P.; Albright, F.; Sulkowitch, H., and Reifenstein, E. C., Jr.: Colorimetric Assay of 17-Ketosteroids in Urine, J. Clin. Endocrinol. **1**:234, 1941.

8. Nathanson, I. T.; Miller, R. B.; Towne, L. E., and Aub, J. C.: The Close Correlation of Androgen and Creatinine Excretion in Normal Children, Endocrinology **28**:866, 1941.

9. Reference has previously been made [1a] to the evidence for this thesis. Since then additional supporting evidence has become available (Talbot, Butler and Berman.[1b] Fraser and others [7]).

during childhood. If this is so, the fact that the output of 17-keto steroids rises as a person changes from a child to an adult implies a relation between the secretory activity of the adrenal cortex and growth and development. Moreover, the continued rise in values for the excretion of 17-keto steroids from 14 to 18 years suggests that the menarche in girls and its equivalent in boys [10] do not necessarily culminate the endocrine development which started several years earlier. On the contrary, puberty appears to be only a milestone on the path from adolescence to maturity.

II. PATIENTS WHOSE GROWTH AND DEVELOPMENT DEVIATE FROM THE AVERAGE

The relation between urinary excretion of 17-keto steroids and growth and development previously discussed has been further investigated by observations on the output of 17-keto steroids of children whose growth and development deviate from the average normal. The present section is subdivided into portions dealing with (1) sexually precocious but otherwise apparently normal children and (2) dwarfed, sexually retarded patients. Observations on children with the precocity of adrenal cortical virilism have been presented elsewhere.[1]

1. Physically Accelerated but Otherwise Apparently Normal Children.—Most children observed in this community do not show gross clinical evidences of sexual development until they reach the age of at least 10 or 11 years.[10] Nevertheless there are a few children whose sexual development and adolescent growth begin a few years earlier and correspond to the average development of children several years older. They are persons who are apparently representative of one extreme of the normal variations encountered in childhood. They show no evidence of the diseases of the gonads, adrenal cortex or central nervous system which are known to cause sexual precocity.[11] Data on 5 such children are listed in table 2. The sex, chronologic age, height, weight and urinary output of 17-keto steroids per day are listed in the sections on the left side of the table. In the sections on the right side is tabulated the "developmental" age [12] of each child as estimated by finding the average

10. Shuttleworth, F. K.: The Adolescent Period, Monograph of the Society for Research in Child Development, 1938, vol. 3, no. 3, serial no. 16. According to Shuttleworth, the average age of the menarche in normal girls is approximately 13 years, while normal boys are believed to attain puberty at approximately 14 years of age.

11. Talbot, F. B., and Talbot, N. B., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1941, vol. 1, chap. 40.

12. The term "developmental" age has been introduced here to serve as a common denominator for comparisons of the developmental status of patients with those of average normal children.

age of normal children who respectively were of the same height,[13] showed the same degree of skeletal maturation [14] and excreted equivalent amounts of 17-keto steroids (table 1).

The heights recorded in table 2 show, as might be expected,[14a] that this group of 5 children tended to be taller than the mean for their chronologic age. They were of approximately normal weight for their height and age.[15] With the exception of the boy (subject 1) their output of 17-keto steroids surpassed that of 9 of every 10 normal children of corresponding chronologic age. However, their excretion of 17-keto steroids did not exceed the normal adult ranges (see chart). The average "developmental" age of these patients estimated by reference to their height (9¾ years), output of 17-keto steroids (12¼ years) and skeletal maturation (10½ years) was advanced over their average chronologic

TABLE 2.—*Observations on Physically Accelerated Children*

Subject No.	Sex	Height, In.	Weight, Lb.	Total 17-Keto Steroids per Day, Mg.	Chronologic Age, Yr.	"Developmental" Age, Estimated from: Height, Yr.	17-Keto Steroid Output, Yr.	Skeletal Development, Yr.
1	M	46	58½	0.8	5	6	7½	7½
		50	67	1.1	6¼	8½	8¼	10¾
2	F	53	80	6.7	7	9	15½	10
3	F	57½	79¾	4.1	7½	11	13	12
		58¾	84½	2.8	8	12	11	..
		60	99¼	7.8	8½	12¼	16½	..
4	F	46½	53¾	3.7	7	6½	12½	8¾
5	F	57	84	4.7	8½	11	13½	13
Average					7¼	9½	12	10½

age of 7¼ years by two and a half, five and three and a half years, respectively.

2. Dwarfed, Sexually Retarded Children.—In contrast to the foregoing accelerated children, table 3 presents observations on 9 patients whose growth was definitely retarded and who showed no external manifestations of sexual maturation. Examination of these patients did not reveal such recognized causes for dwarfism as severe malnutrition,

13. Normal standards of height and weight for children from birth to 6 years of age were obtained from the Department of Child Hygiene, Harvard School of Public Health, and for children from 6 to 16 years from studies made at the University of Iowa.

14. Todd, T. W., and others: Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937.

14a. Richey, H. G.: The Relation of Accelerated, Normal and Retarded Puberty to the Height and Weight of School Children, Monograph of the Society for Research in Child Development, 1937, vol. 2, no. 1, serial no. 8.

15. Baldwin-Wood height-weight-age standards.

chronic infection, congenital malformation, renal disease or hypothyroidism. There was no familial history of dwarfism. On the contrary, younger siblings were taller than the patient in several instances. All of the children appeared to be of approximately normal intelligence. Though it is appreciated that it is difficult to make an accurate diagnosis of hypopituitarism in children unless a definite pituitary lesion has been demonstrated,[16] their presumptive clinical diagnosis was dwarfism and developmental retardation secondary to anterior pituitary insufficiency.

The data of table 3 reveal that these patients were the antithesis of the accelerated children represented in table 2. The abnormal deviations were most clearly evident in patients over 12 years old. In addition to being short in stature, their skeletal development tended to be extremely

TABLE 3.—*Observations on Physically Retarded Children*

Subject No.	Sex	Height, In.	Weight, Lb.	Total 17-Keto Steroids per Day, Mg.	Chronologic Age, Yr.	"Developmental" Age, Estimated from		
						Height, Yr.	17-Keto Steroid Output, Yr.	Skeletal Development, Yr.
6	M	38½	32½	0.2	8½	3½	3½	...
		39¾	37	0.7	10	4	7	6½
7	M	41½	....	0.8	9	4½	7½	7¼
8	F	42¾	43	1.3	11½	4¾	9	7¼
9	M	47½	51½	0.8	12¾	6½	7½	8¾
10	M	42½	43½	1.0	13	4½	8	7½
11	M	54½	58½	1.5	13½	9½	9	10¾
12	M	48¾	....	0.9	15	7	8	9½
		51½	....	0.4	16	8½	5	...
13	M	53	69	0.3	17	9	4	11¾
Average					12¼	6¼	6¾	8½

retarded and their output of 17-keto steroids to be abnormally low. When their "developmental" age was estimated from their height, excretion of 17-keto steroids and skeletal maturation, they were found to be six, five and a half and four years, respectively, behind their average chronologic age of 12¼ years.

3. Comment.—So far as the authors are aware, there are no previous reports on the excretion of 17-keto steroids of tall, accelerated normal children similar to those described here. It is of interest that these children did not excrete more 17-keto steroids than normal older children or adults. This would suggest that they had merely anticipated the normal rise in excretion of 17-keto steroids which usually occurs at an older age. They differed remarkably in this respect from patients with sexual precocity due to hyperplasia of the adrenal cortex or adrenal

16. Such was the case in 1 patient (case 13) of the present series who had a craniopharyngioma.

cortical carcinoma.[1] Even the youngest of the abnormal patients tended to excrete more 17-keto steroids than normal adults.

It would seem to be significant that the "developmental" ages of the accelerated normal subjects estimated from their clinical appearance, height, output of 17-keto steroids and skeletal development all agreed closely. A similar correlation was also found for the children over 12 years old with retarded physical development. These observations suggest that infants and younger children tend to grow and develop up to a certain point without those hormonal stimuli which are manifest by an increased excretion of urinary 17-keto steroids. It would appear

TABLE 4.—*Observations on Obese Children*

Subject No.	Sex	Height, In.	Weight, Lb.	Per Cent Over-weight	Total 17-Keto Steroids per Day, Mg.	Chronologic Age, Yr.	"Developmental" Age, Estimated from: Height, Yr.	17-Keto Steroid Output, Yr.	Skeletal Development, Yr.
					Group A				
14	M	55	104	44	1.1	9	10	8	12
15	M	61¼	140	44	2.8	13	13	11	13¼
16	M	57	117	46	2.1	10	11	10	12
17	M	61	140	46	3.4	12	13	12	..
18	F	53	99	48	0.8	8	9	7½	9
19	F	55	111	50	2.6	11	10	11	11
20	F	59	135	50	2.7	12	12	11	..
21	M	61	148	54	6.8	12	13	16	12
22	F	57	128	56	3.2	12	11	12	11
Average						11	11	11	11½
					Group B				
23	F	60	146	60	2.4	10	12	11	10
24	F	55	120	62	7.7	11	10	16½	15
25	F	63	180	63	8.1	11	14	17	13
26	M	56	129	68	4.2	10	10½	13	13
27	F	59	152	69	4.5	11	12	13	14
28	F	56	150	92	3.8	11	10½	12½	12
29	M	65½	265	134	3.5	9	15	12	14
Average						10½	12	13½	13

that if these stimuli occur at an early age the accelerated growth and development of adolescence occur and precocity results. On the other hand, when these stimuli are late in making their appearance, growth and development proceed only at the preadolescent rate.

III. PATIENTS WITH MISCELLANEOUS CONDITIONS

In this section an attempt is made to determine whether the abnormal growth or development of patients with obesity, with hypothyroidism treated by thyroid therapy or with mongolism may be associated with disorders of glandular function which are reflected by abnormal variations in the urinary output of 17-keto steroids.

1. Obesity.—Table 4 presents observations on 16 fat children of the type most commonly seen by the pediatrician. They were between 44

and 134 per cent overweight by the Baldwin-Wood standards. Their secondary sexual development appeared to be within normal limits. They presented no clinical evidence of endocrine disorder unless obesity per se is considered as such. The data of table 4 are arranged as they are in tables 2 and 3 with the exception that the patients are listed in the order of increasing percentage of overweight rather than according to age. Measurements on the 9 children who were between 44 and 56 per cent overweight are presented in the upper section of the table (group A); data for the 7 children who were from 60 to 134 per cent overweight are given in the lower section of the table (group B).

The height, output of 17-keto steroids and skeletal development of the children of group A tended to be well within normal limits for their respective ages. The output of 17-keto steroids of 1 child in this group (subject 21) was moderately elevated above the normal limits, described by the shaded area in the chart. On the other hand, the children of group B had an average developmental age estimated from their height, output of 17-keto steroids and skeletal development that exceeded their average chronologic age by one and a half, three and two and a half years, respectively. The values for excretion of 17-keto steroids of 5 of the 7 children of group B (subjects 24, 25, 26, 27 and 29) were moderately elevated above the normal ranges, indicated by the shaded area in the chart. There was a tendency for fat children whose excretion of 17-keto steroids was significantly elevated to show the greatest degree of secondary sexual development for their chronologic age.

2. Hypothyroidism.—Measurements on 12 children with hypothyroidism who were between 7 and 15 years of age are presented in table 5. They were receiving between ¾ and 3 grains (0.048 and 0.19 Gm.) of thyroid U. S. P. or its equivalent daily. This medication was sufficient to eliminate symptoms of hypothyroidism, such as increased fatigability, underactivity, constipation, pale, dry skin and sensitivity to cool weather. Some of the patients were mentally retarded. There were no abnormal deviations in secondary sexual development.

It is noted that there was a tendency for these children to be of slightly shorter stature than average for their age. Their weight was within normal limits for their height and age according to the Baldwin-Wood standards. The output of 17-keto steroids by these patients tended to be slightly low; for 3 children (subjects 37, 39 and 42) the values fell below the normal ranges, described by the shaded area of the chart. Their "developmental" age estimated from their height, output of 17-keto steroid and skeletal development was retarded below their chronologic age by an average of two and a half, two and a half and two years, respectively. No relation between the dose of thyroid and this retardation was evident.

3. Mongolism.—The excretion of 17-keto steroids of 13 patients with typical mongolism is presented in table 6. The data show that the excretion was within normal limits for 7 patients, slightly elevated above

TABLE 5.—*Observations on Children with Hypothyroidism Who Were Receiving Thyroid Therapy*

Subject No.	Sex	Height, In.	Weight, Lb.	Thyroid* Dose, Grains	Total 17-Keto Steroids per Day, Mg.	Chronologic Age, Yr.	"Developmental" Age, Estimated from: Height, Yr.	17-Keto Steroid Output, Yr.	Skeletal Development, Yr.
31	F	44	48	¾	0.4	7	5½	5	5
32	F	46½	57	1¼	0.5	7½	6½	6	..
33	F	44	49	1	0.8	9	5½	7½	5¾
34	F	52¾	85	1¼	1.3	9¾	9	9	9¾
35	M	51	65	1	1.0	10½	8½	8	..
36	F	50	57	¾	1.1	11	8	8¼	9
		55	69	3	1.0	11½	10	8	11¼
37	F	..	..	3	1.1	12	..	8¼	..
		54½	65	2	0.2	12½	9½	3†	11
		55½	66	2	2.8	13	10	11	..
38	F	57	73	2	3.4	13½	11	12	..
39	F	53¼	91	2	1.3	12½	9	9	12¼
40	F	60	94	1½	3.0	12¾	12½	11½	..
		52½	74	1½	2.3	14	9	11	11¼
41	F	54½	79	1½	2.8	15	9½	11	13¼
42	F	65¼	146	2	4.6	15½	16	13	..
Average						11¾	9¼	9¼	9¾

* Thyroid U. S. P. or its equivalent.
† Excluded from the average.

TABLE 6.—*Observations on Patients with Mongolism*

Subject No.	Sex	Age, Yr.	Total 17-Keto Steroids per Day, Mg.
43	M	9	2.1
44	F	10½	4.4
45	M	11	1.3
46	M	14	7.2
47	M	15	5.3
48	M	16	10.2
49	M	16	7.3
50	M	18	8.9
51	M	18	5.5
52	F	18	3.0
53	F	18	6.1
54	F	23	3.6
	F	24	4.1
55	M	26	5.3

normal for 1 and depressed below normal for 4. All subjects with low values were over 18 years old. Thus, no definite tendency to a hyperexcretion or a hypoexcretion of 17-keto steroids by patients with this disease is evident from these measurements. It is possible, however, that

a larger series of measurements might reveal that a tendency to hypoexcretion does exist, especially in adult patients with mongolism.

4. Comment.—The present data confirm Bruch's observation [17] that there is a definite tendency for obese children of the constitutional type described here and elsewhere [18] to show advanced skeletal development and to mature somewhat earlier than the average child. Therefore, it is not surprising to note that some of the fat boys and girls showed an elevation in their output of 17-keto steroids similar to that found for the precocious "normal" children of section II. This elevation, which appears to be associated with an acceleration in growth and skeletal development, was much more striking for the very obese children than for the moderately obese. Because children with elevated values for excretion of 17-keto steroids are not necessarily overweight (section II, 2), it seems unlikely that factors responsible for the elevated excretion of 17-keto steroids caused the obesity. However, the data suggest that factors contingent on a high degree of obesity may favor a hyperexcretion of 17-keto steroids and accelerated growth and development.

The observations on the children with hypothyroidism of table 5 also provide information of interest. It appears that the excretion of 17-keto steroids by such patients tends to be low even when they are receiving what appears clinically to be adequate doses of thyroid. Thus, one is left with the possibility that thyroid medication as commonly prescribed is inadequate or that "hypothyroidism" is not necessarily a simple dis ease, which is characterized only by a lack of thyroid hormone. Further studies are needed to support the implication of the present observations concerning an associated diminution in activity of the adrenal cortex.

Although the values for the excretion of 17-keto steroids of the older patients with mongolism were low, those for younger patients were not. Because mongolism is a disease which apparently has its inception before birth, it is difficult to ascribe any etiologic significance to the low values for the excretion of 17-keto steroids of the older patients with mongolism.

SUMMARY

A series of measurements of the urinary excretion of 17-keto steroids have been made on normal subjects ranging in age from a few hours to over 47 years. It was found that the output of 17-keto steroids is low from birth to approximately 10 years. The values for excretion of 17-keto steroids of older children gradually rose as the subjects approached 18 years of age. From the definition of the approximate

17. Bruch, H.: Obesity in Childhood: I. Physical Growth and Development of Obese Children, Am. J. Dis. Child. **58**:457 (Sept.) 1939.

18. Talbot, N. B., and Worcester, J.: The Basal Metabolism of Obese Children, J. Pediat. **16**:146, 1940.

normal range of excretion of 17-keto steroids it is possible to tell whether a given value is abnormally high at any age. On the other hand, because values approximating 0 may be considered normal for children under 10 years of age, detection of abnormally low excretion in children under that age is not possible. However, children who have reached their twelfth birthday should excrete at least 1 mg. of 17-keto steroids daily.

A tendency toward a moderate elevation in output of 17-keto steroids was observed in apparently "normal" children with physiologic sexual precocity and in abnormally overweight children whose development also tended to be accelerated. Abnormally low values for excretion of 17-keto steroids were obtained for children over 12 years old whose growth and development were retarded. Included among these physically retarded children were patients with presumable deficiency of the anterior lobe of the pituitary gland and patients with hypothyroidism who were receiving thyroid therapy. The excretion of 17-keto steroids of patients with mongolism was not consistently abnormal.

RESPIRATORY METABOLISM IN INFANCY AND IN CHILDHOOD

XXVII. REGULATION OF BODY TEMPERATURE OF PREMATURE INFANTS

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Lability of body temperature is a well known characteristic of premature infants, and maintenance of a uniform body temperature is considered an important item in their care. The physician, therefore, should have accurate information on the physiologic factors which contribute to the readiness with which a disturbance of their heat balance may be induced by minor changes in environmental temperature. The present investigation is a quantitative study of the factors concerned in heat regulation, namely, heat production, heat loss by radiation and conduction, heat loss by evaporation, skin temperature, rectal temperature and bodily activity. From the data the conclusion is drawn that healthy premature infants do not suffer, as a group, from a defect in circulatory adjustments to different air temperatures. They do have an inadequate production of sweat, a large surface area and a poor layer of insulating subcutaneous fat for protection against heat loss.

LITERATURE

Previous studies of this subject on infants have included one or more of the pertinent factors, but no publication has come to our attention which reports simultaneous or composite observations of all of the six important items: heat production, heat loss by radiation and conduction, heat loss by evaporation, rectal temperature, skin temperature and activity. Blackfan and Yaglou [1] have clearly demonstrated the

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College. Assistance in this work was given by the Children's Bureau, United States Department of Labor.

1. Blackfan, K. D., and Yaglou, C. P.: The Premature Infant: A Study of the Effects of Atmospheric Conditions on Growth and Development, Am. J. Dis. Child. **46**:1175 (Nov., pt. 2) 1933.

great importance of relative humidity in the well-being of premature infants, and they have included data on the lability of their body temperature. Talbot [2] has also recorded important measurements of their skin temperature. However, such measurements alone are of limited value as an indicator of the state of the circulation, since they are influenced by other factors, including the amount of heat being produced, the conductivity of the tissues beneath the skin, the rate of evaporation of water and the air temperature. Mordhorst [3] showed that premature infants increase their heat production in cool air, and he attributed this augmentation to a chemical stimulation of metabolism. Eckstein [4] described interesting experiments in which he placed a strain on the heat-regulating mechanism by putting infants in baths at various temperatures. His conclusion from these observations is that premature infants have no important defect in their physiologic responses to different environmental temperatures.

Reported studies of body temperature for infants are less complete than for adults, despite an equal or greater practical need for such studies. The methods elaborated for adults by Burton,[5] by Winslow, Herrington and Gagge [6] and especially by Hardy and Soderstrom [7] have served as a guide in our studies. Their conclusions are briefly presented as a means of properly evaluating the present work on premature infants.

From the point of view of physiologic reactions, the range of air temperatures from 22 to 35 C. may be divided into three zones. Below 28 or 29 C. lies the zone of body cooling. Within this range of air temperature the active and normally clothed person frequently feels uncomfortably warm, whereas the unclothed and motionless adult gradually loses heat, with a resultant fall in body temperature which is eventually arrested by a chill accompanied by muscular activity and a rise in heat production. In this zone vasoconstriction is at a maximum; evaporation is at a minimum, and heat production in adult

2. Talbot, F. B.: Skin Temperatures of Children, Am. J. Dis. Child. **42**: 965 (Oct., pt. 2) 1931.

3. Mordhorst, H.: Ueber die chemische Wärmeregulation frühgeborener Säuglinge, Monatschr. f. Kinderh. **55**:174, 1932.

4. Eckstein, A.: Ueber die Wärmeregulierung der frühgeburten, Ztschr. f. Kinderh. **42**:5, 1926.

5. Burton, A. C.: The Application of the Theory of Heat Flow to the Study of Energy Metabolism, J. Nutrition **7**:497, 1934.

6. Winslow, C.-E. A.; Herrington, L. P., and Gagge, A. P.: Physiological Reactions of the Human Body to Varying Environmental Temperatures, Am. J. Physiol. **120**:1, 1937.

7. Hardy, J. D., and Soderstrom, G. F.: Heat Loss from the Nude Body and Peripheral Blood Flow at Temperature of 22° C. to 35° C., J. Nutrition **16**:493, 1938.

male subjects is constant in the absence of muscular movement or a chill. The body cools like an inert physical mass.

Above 30 C. (86 F.) lies the zone of evaporative regulation. Active sweating occurs, and it carries most of the burden of heat loss. In addition, circulation through the dilated small vessels of the skin is rapid, and heat is thereby brought to the surface for dissipation to the air. This increase in circulation raises, as it were, the conductivity of the body tissues. This parallelism, as will be brought out later, is utilized by these authors to measure the circulation itself from measurements of the conductivity of the tissues.

The third zone, that of circulatory regulation, is narrow, lying between 28 or 29 C. and 30 C. Only in this range does vasomotor control alone, unassisted by sweating, succeed in regulating body temperature. This is an important and seldom appreciated fact. It is obvious that an unclothed subject with a defective sweating mechanism and with defective muscular development would find his circulatory system inadequate to maintain a uniform body temperature outside the narrow limits of this zone of vasomotor control. Since the premature infant is defective in both these respects, it is clear that no matter how good his circulation, changes in his body temperature cannot be prevented in the presence of even minor variations in air temperature. Such fluctuations are, therefore, not good evidence of inadequate vasomotor control in premature infants. The type of study reported in the present work, in which the circulation is studied by means of calculations of the actual thermal conductivity of the tissues, permits an evaluation of circulatory control.

METHODS

Subjects.—Twenty-five male premature infants were studied. The average weight at the time of observation was 2,258 Gm. All weighed less than 2,500 Gm. at birth. At the time of observation their ages ranged between 4 and 53 days and their weights between 1,440 and 2,900 Gm. Since they were thriving during the periods of study, the results cannot be extended without reserve to very feeble, sick or smaller infants.

Prior to observations the infants resided in an air-conditioned nursery maintained at a temperature of 24.5 C. Suitable clothing and additional local heat if necessary served to maintain a comparatively steady rectal temperature of about 37 C. (98.6 F.).

Diet.—The infants were given conventional diets of human milk or evaporated or half-skimmed cow's milk,[8] containing between 100 and 125 calories per kilogram of body weight.

8. Powers, G. F.: Comparison and Interpretation on a Caloric Basis of the Milk Mixtures Used in Infant Feeding, Am. J. Dis. Child. **30**:453 (Oct.) 1925; Infant Feeding: Historical Background and Modern Practice, J. A. M. A. **105**:753 (Sept. 7) 1935.

Experimental Procedure.—Immediately after a feeding, the infant was placed on a special bed within the calorimeter chamber. He was fastened snugly but not uncomfortably to this bed by a cotton belt which covered the lower half of the abdomen and the hips. The legs were secured at the ankles by adhesive tape. A glass tube for collection of urine under oil was then tied in place by another cotton belt overlapping the restraining belt. The rectal thermometer was inserted and secured with two narrow bands of adhesive tape. The four skin thermocouples were then affixed with collodion to the left heel, shin and axilla and left side of the abdomen. The interval between the beginning of the feeding and the completion of these preparations varied from thirty to sixty minutes.

After completion of these preliminary steps, the skin temperature was measured with the radiometer as described hereinafter, and the calorimeter closed. The infant remained in the calorimeter after closure of the lid for one hundred and fifteen minutes, divided into a preliminary period of forty-five minutes (during which adjustments of the oxygen content of the air, of humidity and of the physiologic status of the baby occurred) and two experimental periods of thirty-five minutes each. In some cases, as noted in table 2, the final thirty-five minute period was omitted, and in other cases the periods were shortened. As noted in the table, not every observation was complete in all details. In all, 53 observations were made for a total of 89 experimental periods, most of which were thirty-five minutes in length.

At the termination of the final period, the calorimeter cover was removed, the skin temperature again measured by the radiometer and the skin inspected for visible perspiration. The position of the rectal thermocouple was also noted.

A brief description of the measurements which were made follows:

1. Heat Production: An open circuit apparatus fully described elsewhere[9] was employed and the heat production calculated from the oxygen consumed and the carbon dioxide produced. Alcohol checks for the year are displayed in table 1.

2. Heat Loss by Evaporation: Air entering the calorimeter chamber was dried by passage over calcium chloride. Evaporated water was collected and measured by passing the outgoing air through weighed bottles of sulfuric acid. The ventilation rate was adjusted for each baby so that there was a uniform water content of the air within the calorimeter chamber during each experimental period. The relative humidity was usually between 50 and 60 per cent but was somewhat higher in the case of subjects who perspired actively.

3. Heat Loss by Radiation and Conduction: Direct measurement of these two avenues of heat loss taken together was made by means of the technic described in a previous publication.[10] As described in that paper, the respiratory chamber was converted into a so-called direct calorimeter by the placement of thermocouples near the inside and outside surfaces of the copper walls of the chamber. By calibrating the calorimeter with known sources of heat, the temperature gradient between these two sets of thermocouples was used to calculate the rate of heat flow from the calorimeter and from the source of heat within it. Alcohol checks for the experimental year are displayed in table 1, and they serve as a check on the reliability of the method. Since, however, infants were in various states of activity, which caused

9. Gordon, H. H.; Levine, S. Z.; Deamer, W. C., and McNamara, H.: Respiratory Metabolism in Infancy and in Childhood: XXIII. Daily Energy Requirements of Premature Infants, Am. J. Dis. Child. **59**:1185 (June) 1940.

10. Day, R., and Hardy, J. D.: Respiratory Metabolism in Infancy and in Childhood: XXVI. A Calorimeter for Measuring the Heat Loss of Premature Infants, Am. J. Dis. Child. **63**:1086 (June) 1942.

irregular currents of air within the chamber, an additional check on the accuracy of the measurements of heat loss is desirable. Only an indirect estimation of the magnitude of this source of error can be made by comparing the figures for the calculation of heat production by the conventional method of gas analysis with those obtained by adding the figures for loss by radiation and conduction, evaporation and loss or gain through storage or loss of body heat as indicated by change in temperature. The degree of reliability of the measurements of heat production may be gaged by the alcohol checks, although with irregular crying during a period the error might become greater, a fact which must be borne in mind when one proposes, as in the present analysis, to use calculations of heat production as a yardstick for the accuracy of measurements of heat loss. Futhermore, measurements of loss

TABLE 1.—*Alcohol Checks for the Experimental Year*
The Figures Indicate Calories per Hour. Each Period Was 35 Minutes Long

	Heat Loss						Heat Production		
	Radiation and Conduction			Evaporation					
Date	Observed	Theoretic *	Percentage Difference	Observed	Theoretic	Percentage Difference	Calculated from O_2 Burned (Observed)	Calculated from Alcohol Used (Theoretic)	Percentage Difference
3/10/41.....	8.90	9.37	— 5.0	....	1.13	....	10.23	10.50	—2.6
	7.36	7.76	— 5.2	....	0.94	....	8.05	8.70	—7.5
5/12/41.....	3.37	3.47	— 2.9	0.59	0.42	40.5 †	3.73	3.89	—4.1
	3.32	3.38	— 1.8	0.57	0.41	39.0	3.49	3.79	—7.9
9/10/41.....	5.92	5.58	6.1	0.71	0.67	6.0	6.01	6.25	—3.8
9/17/41.....	3.22	3.56	— 9.6	0.53	0.43	23.3	3.88	3.99	—2.8
	3.43	4.07	—15.7	0.52	0.49	6.1	4.17	4.56	—8.6
10/16/41.....	4.65	4.34	7.1	0.51	0.52	—1.9	4.85	4.86	—0.2
	4.62	4.25	8.7	0.52	0.51	2.0	4.51	4.76	—5.3
1/20/42.....	4.18	3.93	6.4	0.48	0.47	2.1	4.12	4.40	—6.4
	4.00	3.79	5.5	0.47	0.46	2.2	3.98	4.25	—6.4

* This figure is obtained by subtracting the theoretic loss by evaporation from the theoretic heat production.

† In 30 consecutive checks prior to the experimental year the average deviation of the observed water output from the theoretical was 9.5 per cent, and 24 of the 30 observations deviated by less than 15 per cent.

of heat by radiation and conduction, which forms about 65 to 70 per cent, and by evaporation, which contributes perhaps 25 per cent of the total, and the loss or gain by body shifts of heat, which contributes the remainder, all have their own inherent errors. The loss or gain by storage as calculated from changes of cutaneous and rectal temperature is probably highly inaccurate. With these considerations in mind, one is in a position to evaluate better the results shown in chart 1. In this graph the two methods of calculating heat production are compared. The coefficient of correlation is 0.87 ± 0.02. The probable error of estimate of heat production calculated from gas analysis is 5.1 calories per kilogram per twenty-four hours. The mean value for heat production in these 50 observations is 70.9 calories per kilogram per twenty-four hours. The probable error of estimate for heat production calculated from heat loss and storage is 4.7 calories, and the mean value, 70.4. Of these 50 pairs of observations, 23 showed a difference between the two of 5 per cent or less of heat production; 33 had a difference of 10 per cent or less, and 42, of 15 per cent or less. Of the grand total of 53 observations, 3 were incomplete, so that the comparison could not be made.

From these facts the conclusion is drawn that the two methods of determining heat production have about the same degree of experimental error. This error is small enough to permit conclusions about the group of infants as a whole, but it is too large to warrant speculation about any one infant.

In addition to the error of measurement that occurs from experiment to experiment, there is also the possibility of a systematic error. In the section on "storage" it is shown that the calculation of storage from cutaneous and rectal temperature involves the addition of a constant of 2.77 calories per kilogram per twenty-four hours. Whether this systematic error arises in the measurement of cutaneous and rectal temperature or in the determination of heat loss cannot be determined.

4. Activity: An observer recorded the number of minutes of each period in which the infant was asleep and quiet, asleep and restless, awake and quiet and

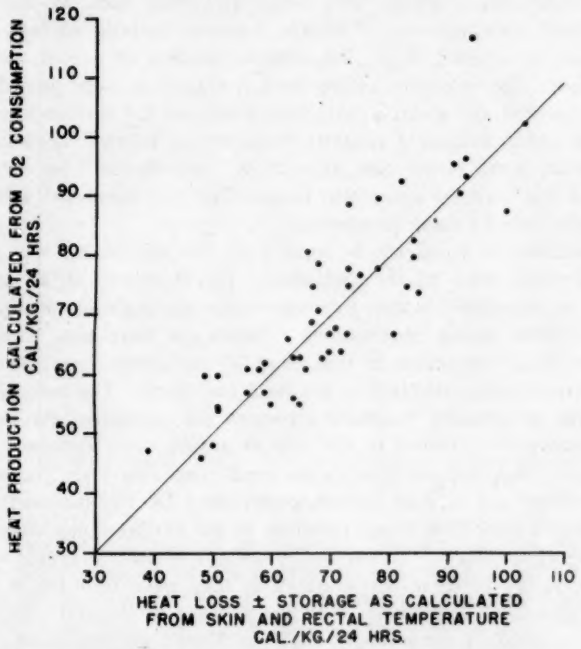

Chart 1.—The relationship between heat production calculated from oxygen consumption and total heat loss ± storage of heat in the body as indicated by changes in rectal and skin temperatures. Failure of the points to fall exactly on the line of perfect agreement is the result of experimental error.

awake and crying. In table 2 and in the analysis of the data, only the number of minutes asleep in relation to the period as a whole has been used as a criterion of activity.

5. Rectal Temperature: A thermocouple coated with latex rubber was inserted 3 or 4 cm. into the rectum and secured to the buttocks with adhesive tape. The temperature of this thermocouple was recorded every five minutes during the experiment. Sharp irregularities in the curve of rectal temperature were frequently produced when the infant moved, cried or had a bowel movement. Such changes were considered to be unrepresentative of shifts in the inner body tem-

perature and were accordingly eliminated by visual smoothing of the curves of rectal temperature.

6. Skin Temperature: Measurements of skin temperature were made in two ways: by means of four thermocouples attached to the skin and leading to a micromax recorder during calorimeter observations, and by means of the Hardy radiometer [11] prior to the beginning of preliminary periods and immediately after the calorimeter was opened at the end of observations. The original intention of using the two sets of figures obtained with the radiometer for indicating changes in skin temperature during periods of observation proved to be invalid, since changes in skin temperature during the preliminary period of adjustment were too great to permit this comparison. Reliance for measurement of changes in skin temperature during the observation period was therefore placed on the thermocouples, the final radiometer readings serving as a base line.

The radiometer measurements were made at twelve sites, as follows: forehead, cheek, chest, abdomen, deltoid muscle, forearm, anterior surface of a hand, posterior surface of a hand, thigh, leg, anterior surface of a foot and posterior surface of a foot. These twelve values were averaged in pairs according to the body area represented and given a weighting based on the surface area measurements of Klein and Scammon [12] (slightly modified) as follows: head 22 per cent, trunk 32 per cent, arms 14 per cent, legs 26 per cent, hands 3 per cent and feet 3 per cent. In this way the mean skin temperature was computed with due consideration to the infant's body proportions.

Since the radiometer could not be used while the calorimeter was closed and since readings made prior to the preliminary period proved to be valueless, it was necessary, as mentioned before, to resort to thermocouples to measure changes in skin temperature during observations. Handicaps were also encountered in the use of the latter apparatus in that most of the infants were able to move or pull off thermocouples attached to the head and arms. The recorded data for changes of skin temperature therefore represent the measurements secured with the four thermocouples attached to the sole of a foot, shin, abdomen and axilla. The proper weighting of these four values on the basis of body proportions was a difficult problem, and it was further complicated by the inconsistent way in which some infants held their arms, resulting in the axilla's being closed at times and open to the air at others. It was finally decided to make a simple arithmetical average of the values of these temperatures as they were recorded at the beginning of each period for comparison with the average at the end. In support of this arbitrary method, a surprisingly high coefficient of correlation, of 0.92 ± 0.02, was found between pairs of average skin temperature values as measured by the radiometer and by the thermocouples in twenty-five simultaneous observations. Since the maximal change of skin temperature took place in the preliminary period, the validity of the average measurements of skin temperature as obtained by this combined radiometer and thermocouple method is considered sufficient for the purpose intended.

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11. Hardy, J. D., and Soderstrom, G. F.: An Improved Apparatus for Measuring Surface and Body Temperature, Rev. Scient. Instruments **8**:419, 1937.

12. Klein, A. D., and Scammon, R. E.: The Regional Growth in Surface Area of the Human Body in Prenatal Life, Proc. Soc. Exper. Biol. & Med. **27**:463, 1930. The total surface area was calculated from the formula: Surface $= 5.88 \times \text{weight}^{0.75}$, as given by A. D. Klein and R. E. Seammon (Relations Between Surface Area, Weight and Length of the Human Body in Prenatal Life, ibid. **27**:456, 1930).

7. Movement of Air: The velocity of turbulent movement of air within the calorimeter in the absence of the baby was measured by a Pierce hot wire anemometer.[13] It varied between 6 and 9 feet (1.8 and 2.7 meters) per minute. This information cannot be used, however, to calculate the proportion of heat lost by convection alone, because of the irregular and unmeasurable bodily activity displayed by the infants.

8. Wall Temperature: The walls surrounding the infant were sheets of copper which were at air temperature.

RESULTS AND COMMENT

The detailed data appear in table 2.

Heat Production.—Chart 2 portrays the values for total heat production obtained in the 89 periods related to air temperature. Ten of

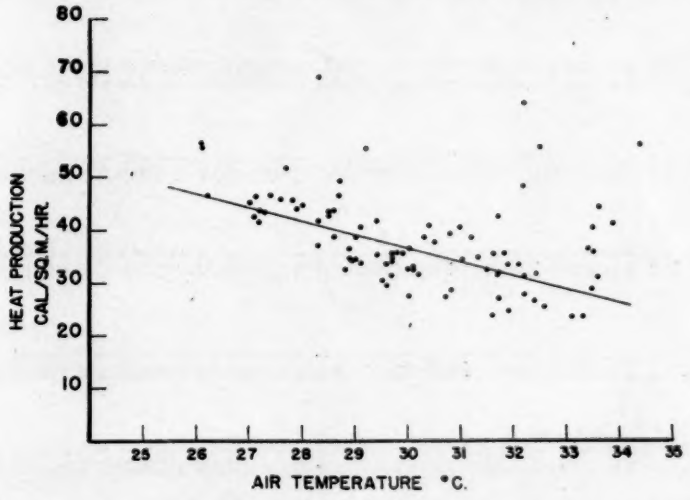

Chart 2.—The relationship between air temperature and the production of heat. In the calculation of the regression line, those periods were omitted in which the infant perspired actively. In infants who perspired, there was a great elevation of heat production due to hard crying. These periods are indicated by open circles. (See text.)

these observations differed widely from the others. In these 10 the infants cried with much more than ordinary vigor, they perspired visibly and they frequently placed their hands or feet against the copper walls of the calorimeter. Accordingly, in the calculation of the regression line for heat production and for heat loss by radiation and conduction (chart 4) these 10 observations were omitted. In charts 2, 3, 4 and 8 these 10 observations are indicated by open circles. It is probable that the precaution of omitting them from the regression line was not entirely necessary, since inclusion of them would not have altered the appearance of the curves to any great extent.

13. Made by the John B. Pierce Laboratory of Hygiene, New Haven, Conn.

TABLE 2.—*Detailed Data*

Infant	Age, Days	Weight, Gm.	Surface Area, Sq. M.	Period, Minutes	Air Temperature, Degrees, C.	Heat Production, Cal./Hr./Sq. M.	Heat Loss, Cal./Hr./Sq. M.		Temperature Change, Degrees C./Hr.		Average Temperature, Degrees C.		Minutes Asleep	Conductance, Cal./Sq. M./Hr./Degrees C.
							Rad.+ Cond.	Evap.	Rectal	Skin	Rectal	Skin		
1	11	2,380	0.177	35	29.7	35.5	23.0	10.8	0.50	0.51	35.95	34.33	35.0	20.5
				36	29.9	35.6	21.7	10.5	0.00	0.51	36.15	34.33	24.0	17.7
2	7	1,958	0.153	30	30.0	32.7	20.9	11.2	0.00	0.70	35.96	34.91	30.0	30.7
				30	30.1	32.2	21.7	11.4	0.00	—0.17	35.96	35.06	30.0	36.8
3	11	2,128	0.163	30	31.2	38.4	17.1	11.3	0.51	0.69	36.85	36.45	14.5	71.0
	13	2,200	0.167	35	29.4	35.1	25.1	8.6	0.00	0.68	36.67	34.47	28.5	15.3
	14	2,250	0.170	35	28.6	38.9	26.8	8.7	0.50	....	36.44	34.30	16.5	16.8
4	28	2,300	0.173	33	30.1	33.0	26.7	10.2	0.00	0.69	37.11	34.40	31.0	13.6
				40	30.4	40.9	32.1	11.6	0.00	0.51	37.16	34.80	13.5	18.9
	34	2,720	0.196	35	30.3	38.4	20.3	10.7	0.39	0.51	36.94	34.65	35.0	13.4
				35	30.5	37.6	20.6	10.9	0.05	0.34	37.04	34.90	35.0	14.7
	36	2,800	0.199	35	28.5	43.4	31.9	11.1	0.36	0.51	36.75	33.55	35.0	14.3
	37	2,800	0.199	35	26.2	46.6	46.7	10.8	—0.48	—0.34	36.91	34.00	28.0	19.7
				24	26.1	56.4	49.8	11.9	—0.10	0.07	36.47	34.00	16.0	25.0
5	8	2,020	0.156	35	29.6	33.2	14.8	9.7	0.00	0.17	36.50	33.97	35.0	9.7
				35	29.7	31.1	15.5	8.9	0.00	0.00	36.50	33.97	34.5	9.5
	12	2,156	0.164	35	29.7	34.0	16.6	9.0	....	0.34	36.80	34.60	35.0	11.7
				35	29.7	34.8	17.0	9.3	....	0.00	36.80	34.70	33.0	12.3
6	32	2,560	0.187	35	28.6	43.5	23.5	9.6	0.16	0.34	36.89	34.96	33.0	17.1
				30	28.7	46.4	23.6	11.2	0.17	0.51	36.97	35.08	16.5	18.5
7	16	2,486	0.183	35	27.3	43.4	30.7	9.7	0.26	—0.17	37.38	34.50	22.0	14.0
				35	27.2	41.4	27.8	9.7	0.00	0.17	37.44	37.50	35.0	12.8
	21	2,610	0.189	35	26.1	55.8	35.9	12.1	0.30	0.34	37.21	33.80	17.0	14.1
	23	2,700	0.194	35	30.8	39.1	17.6	12.0	0.54	0.86	37.24	35.34	31.5	15.6
				35	31.0	40.5	19.0	12.0	0.27	0.34	37.54	35.69	35.0	16.8
	24	2,770	0.198	35	32.5	55.8	21.3	16.8	0.47	0.69	37.67	35.45	22.0	17.2
				35	32.2	48.7	17.0	24.0	0.00	0.17	37.78	35.70	30.0	19.7
8	7	2,320	0.174	35	31.7	31.6	8.6	13.8	0.30	1.03	36.93	35.28	35.0	13.7
	8	2,320	0.174	35	31.9	33.3	12.8	12.4	0.35	0.84	37.02	34.98	31.0	12.4
				35	32.2	27.7	14.3	10.8	0.00	1.20	37.12	35.63	35.0	16 9
	12	2,350	0.176	35	27.1	46.1	32.6	10.9	0.00	0.34	36.98	33.30	22.0	11.8
9	9	2,440	0.180	35	32.4	31.4	13.9	18.9	0.00	0.34	37.32	36.40	35.0	35.7
10	17	1,520	0.126	35	33.5	28.8	5.8	10.7	0.45	0.86	37.22	36.10	26.0	14.6
				35	33.6	31.0	6.0	12.4	0.45	0.66	37.46	36.60	24.5	21.6
	18	1,560	0.129	35	28.9	36.4	21.9	10.0	0.00	0.00	36.23	34.22	23.5	15.9
				30	29.0	38.5	21.5	11.9	0.10	—0.17	36.24	34.22	13.5	16.5
	32	2,000	0.155	30	33.9	41.2	11.9	11.9	1.80	1.90	37.22	35.90	11.0	18.0
				30	34.4	56.3	16.3	21.3	1.30	0.51	37.83	36.55	14.0	29.4
	38	2,300	0.173	35	27.6	45.8	30.4	....	0.10	0.96	36.81	34.75	21.0	21.0
				35	27.7	51.8	30.7	13.2	0.29	0.86	36.90	35.25	19.0	27.1
	53	2,900	0.205	31	28.3	69.1	28.6	18.7	0.21	0.94	37.34	35.05	5.0	20.6
11	4	2,134	0.163	32	28.3	37.0	27.9	....	0.00	—0.17	36.53	34.24	31.0	16.6
	7	2,282	0.172	35	28.7	49.1	23.0	12.7	0.12	0.60	36.88	34.65	7.5	15.8

12.....	17	2,004	0.155	27	29.2	55.4	33.3	17.6	0.23	0.24	36.82	35.04	16.0	28.2
13.....	12	2,016	0.156	23.5	29.4	41.8	22.5	11.3	....	0.17	36.10	33.49	4.0	12.9
14.....	9	2,120	0.162	35	30.0	36.1	23.9	9.2	0.06	0.17	36.70	34.75	31.0	17.0
				35	30.2	31.4	24.1	8.7	—0.20	0.34	36.67	34.80	35.0	17.5
15.....	7	2,212	0.167	35	29.5	30.1	18.9	9.9	—0.25	0.00	35.84	34.08	35.0	16.3
				35	29.6	29.3	17.9	10.2	—0.19	0.00	35.76	34.08	35.0	16.7
	9	2,256	0.170	35	29.1	40.5	23.2	11.4	0.90	0.10	36.43	34.10	16.0	14.9
				35	29.1	33.9	20.1	10.9	0.51	0.07	36.60	34.18	30.5	12.8
16.....	4	2,178	0.166	35	28.9	34.6	16.8	9.8	0.24	0.34	35.96	33.86	22.5	17.7
				35	28.8	32.9	19.5	10.0	0.11	0.24	36.05	34.05	12.0	14.8
	5	2,210	0.168	35	29.0	34.5	21.5	11.0	0.00	0.29	35.51	34.10	9.0	24.5
				35	28.9	34.5	22.3	10.4	0.00	0.17	35.51	34.25	19.0	25.9
	6	2,240	0.169	35	31.6	35.6	14.1	10.5	0.56	0.86	36.59	35.13	31.0	16.9
				35	31.7	31.9	12.8	10.5	0.39	0.35	36.78	35.53	35.0	18.9
17.....	4	2,168	0.165	35	30.0	27.3	23.6	9.0	0.24	0.00	35.95	34.34	32.5	20.3
				35	29.8	35.8	26.1	10.3	0.19	0.17	36.03	34.34	20.5	21.8
	5	2,132	0.163	40	31.8	35.5	17.4	11.2	0.69	0.86	36.87	35.45	21.5	20.2
				31	31.9	24.5	19.0	10.7	0.00	0.00	37.02	35.70	30.0	22.5
18.....	5	1,780	0.143	35	30.7	27.1	12.4	12.0	0.00	0.00	36.20	34.88	23.5	18.5
				35	30.8	28.5	12.8	12.2	0.00	0.00	36.20	34.88	17.0	18.9
	10	1,800	0.147	35	31.3	34.9	21.2	10.1	0.28	0.51	36.73	35.11	12.0	19.3
				35	31.5	32.4	22.0	10.1	0.37	0.39	36.89	35.34	25.0	20.7
19.....	4	2,330	0.174	35	31.7	42.2	16.9	16.1	0.55	0.86	37.26	34.45	15.0	11.7
				21	32.2	64.0	22.5	20.2	0.86	1.37	37.65	35.10	0.0	16.8
	5	2,332	0.174	35	27.4	46.6	29.9	11.8	0.31	0.07	36.29	34.50	11.5	23.3
20..... ...	6	2,348	0.176	35	27.9	44.0	32.8	9.1	0.00	0.45	36.20	34.07	35.0	19.7
				35	28.0	44.7	33.7	9.1	0.00	0.50	36.20	34.35	35.0	23.2
	7	2,432	0.180	32	31.0	34.4	15.9	10.2	0.14	0.63	36.76	35.31	32.0	18.0
	8	2,446	0.180	35	27.0	45.1	28.4	11.1	0.39	0.41	36.34	33.61	35.0	14.4
				35	27.1	42.3	28.8	9.1	0.26	0.05	36.52	33.77	35.0	13.8
21.....	8	2,206	0.167	35	31.6	23.8	10.5	10.2	—0.17	1.03	36.25	35.11	35.0	18.1
				35	31.7	27.2	9.8	9.6	0.00	0.57	36.20	35.58	35.0	31.2
	9	2,236	0.169	35	27.8	45.7	22.5	10.9	0.00	0.29	36.60	34.51	7.0	16.0
	10	2,312	0.173	35	32.4	26.5	8.0	8.3	0.00	0.86	36.58	35.79	35.0	20.7
				40	32.6	25.1	7.7	8.7	0.00	0.51	36.58	36.19	40.0	42.1
22.....	16	2,412	0.179	35	32.1	33.3	12.4	8.7	0.51	1.54	36.67	35.25	35.0	14.8
				35	32.2	31.1	13.0	9.9	0.31	0.86	36.91	35.95	35.0	23.9
	17	2,454	0.181	35	28.3	41.8	33.2	8.7	0.00	0.34	36.42	34.62	35.0	23.3
				35	28.5	42.7	34.9	8.7	0.31	0.22	36.54	34.78	32.0	24.8
23.....	30	1,998	0.155	35	33.4	36.2	19.3	11.0	0.51	0.57	37.15	36.77	35.0	79.6
				35	33.5	35.9	20.0	11.4	0.26	0.34	37.77	37.02	35.0	41.9
24.....	10	2,246	0.170	35	33.5	40.1	14.3	22.6	0.00	0.17	37.30	35.22	27.0	17.8
				25	33.6	44.2	14.7	23.6	0.00	0.57	37.30	35.42	25.0	20.4
	11	2,278	0.171	35	27.2	43.5	30.5	8.7	0.00	0.00	35.60	34.58	19.5	38.3
25.....	14	1,442	0.122	35	33.1	23.3	14.8	8.5	0.00	0.29	36.40	36.01	34.0	59.6
				35	33.3	23.4	12.9	9.3	0.00	0.05	36.40	36.10	29.5	73.8

In the calculation of the regression line of chart 2 and also of chart 4 the assumption has been made that the distribution of the points is linear.

The graph shows that heat production is greater in cool air than in warm air, which confirms the statement of Mordhorst.[3] For men, Hardy and Soderstrom [7] and Winslow, Herrington and Gagge [6] did not find such a relationship, although women may differ in this respect.[14] Two questions arise in connection with the demonstrated inverse correlation between heat production and air temperature in premature infants. Is the relation dependent on factors other than air temperature, such as body weight, which may influence heat production? Furthermore, if the relationship is maintained after exclusion of such factors, is it the result of a true so-called chemical stimulation of heat production or is it the result of crying and bodily activitiy provoked by the cool air?

Since a relationship is known to exist between heat production and body weight and since larger infants were more frequently studied at the lower air temperatures as the natural result of a hesitancy to expose smaller infants to the hazard of chilling, it was found necessary to exclude body weight as a fortuitous factor in the apparent action of cool air in provoking a rise in heat production. This was achieved by calculating the partial coefficient of correlation of heat production and air temperature when body weight was held constant. The value was found to be -0.57 ± 0.05, the negative sign indicating, of course, that heat production was high when air temperature was low. The degree of correlation is significant but not of a high order. The next question concerns the degree of relationship between muscular activity and air temperature. The degree of activity and inactivity was measured by noting the percentage of time during which the infant was asleep. Obviously, an indirect measure of muscular activity such as this is crude, and from the statistical point of view the danger of drawing conclusions from the analysis to follow is increased by the fact that the distribution curve for activity as thus measured is skewed. However, to complete this line of thinking, the partial coefficient of correlation between the percentage of time asleep and air temperature, with body weight held constant, was 0.38 ± 0.07. Obviously, in order to determine if true chemical regulation occurs, both the percentage of time asleep and the body weight must be eliminated from the actually found crude relationship of air temperature and heat production. Accordingly, a partial coefficient of correlation between air temperature and heat production, holding both percentage of time asleep and body weight constant, was calculated and found to be -0.47 ± 0.06. At first glance this poor but nevertheless significant relationship suggests the existence of chemical regulation, but such a conclusion is unwarranted because of the inade-

14. Hardy, J. D.; Milhorat, A. T., and DuBois, E. F.: Basal Metabolism and Heat Loss of Young Women at Temperatures from 22° C. to 33° C., J. Nutrition **21**:383, 1941.

quacy of the method used to measure activity and the existence of possible unknown factors. The question of chemical regulation, then, remains open, and it requires for solution some good method of measuring or of preventing muscular activity.

Although these figures indicate a protective elevation of metabolism in cool air, it is highly probable that full term infants would show an even greater elevation. Gordon and co-workers [9] found that under average conditions of activity throughout the twenty-four hours the total metabolism of premature infants was only 18 per cent above the basal level while full term infants could elevate the rate of heat production by 40 per cent under similar conditions.

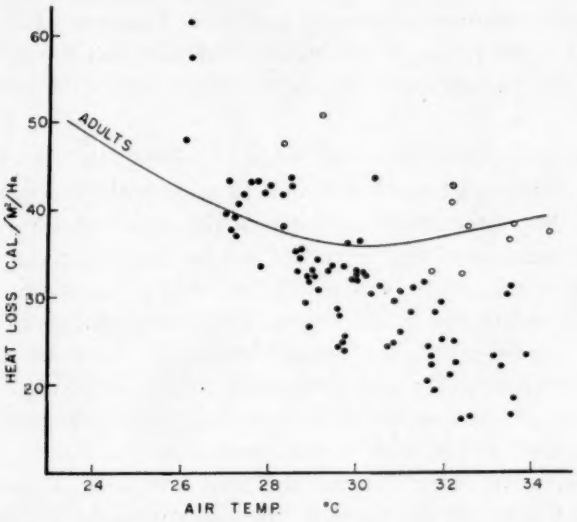

Chart 3.—The relationship between total heat loss and air temperature. The open circles indicate experimental periods in which the infant perspired actively. The adult curve used for comparison is drawn according to the data of Hardy and Soderstrom.[7]

Total Heat Loss.—Chart 3 portrays the values for total heat loss obtained in the eighty-nine periods expressed in calories per square meter per hour. For comparison, a line drawn through similar data of Hardy and Soderstrom [7] for 2 men has been placed in the chart. Open circles represent periods in which active perspiration was noted. In these observations 16 to 24 calories per square meter per hour was lost by evaporation. Undoubtedly, active perspiration was present in a number of instances in which less than this number of calories was lost by evaporation, but this figure was deemed suitable for adequately separating the instances in which heat loss by this route was significantly elevated.

The curve for adults illustrates some of the points brought out in the introductory portion of this paper. The elevated heat loss in cool air is the result of increased loss by radiation and conduction; in warm air it is the result of sweating. The metabolic rate of the adults did not vary at the different air temperatures, in contrast to the results for premature infants reported in the preceding section.

The points for the infants show that only those who perspired had a heat loss similar to that of the adults in warm air and that most of the values at air temperatures of 30 C. and above fell well below the adult figures. In cool air, on the other hand, the infants lost more heat per unit of skin area than the adults. A possible explanation for these differences between the infants and the 2 adult men might be that in warm air vasodilatation is inadequate and hence heat loss small, whereas in cool air vasoconstriction is inadequate and heat loss too great. The reasons why this explanation is not acceptable appear in the two following sections.

Radiation and Conduction.—If there is a defect in the circulatory reactions of premature infants sufficient to disturb the balance between heat loss and heat production, evidence of this defect should be obtainable by proper analysis of the figures for loss by radiation and conduction. Loss of heat by this route is dependent on skin temperature, which in turn is greatly influenced by the flow of blood through the small vessels of the skin. Since, as shown before (chart 3), there are significant differences between adults and premature infants with regard to loss by evaporation of water in warm air and since these differences are not necessarily related to the state of the circulation, the figures for radiation and conduction alone and not for total heat loss are used in the analysis. In a later section entitled "thermal conductivity" the state of the circulation is examined by a different method which permits use of figures for total heat loss. The present section, in which figures for loss of water are omitted, and the section on thermal conductivity supplement one another, and the conclusions arrived at in each section are similar. By both methods of analysis, the circulatory responses of the infants are found to be similar to those of adults.

In air temperatures below 30 C. loss by radiation and conduction in adults forms a progressively larger proportion of the total loss; vasoconstriction is believed to be maximal, and the water loss is the result, not of active sweating, but of insensible perspiration.[7] Chart 4 shows the actual values obtained for the group of infants at different air temperatures for loss by radiation and conduction per square meter of body surface. The regression line shown in the chart was calculated on the assumption that the distribution is linear. So that one can make a fair comparison with the figures for heat production (chart 2), the

regression line was calculated with the exclusion of the 10 observations (open circles in the charts) in which there was excessive crying, as mentioned in the section on "Heat Production." The dotted line in chart 4 represents the regression line corrected for the possible systematic error discussed under "Heat Loss by Radiation and Conduction" in the section on methods and to be treated later under "Storage."

The points for the infants are seen to be distributed in a linear fashion within a broad zone, the position and slope of which correspond surprisingly closely to the adult curve. The adult curve is calculated from the data of Hardy and Soderstrom.[7] It is not a straight line. The major inflection is a downward one in air temperatures above 31 C.

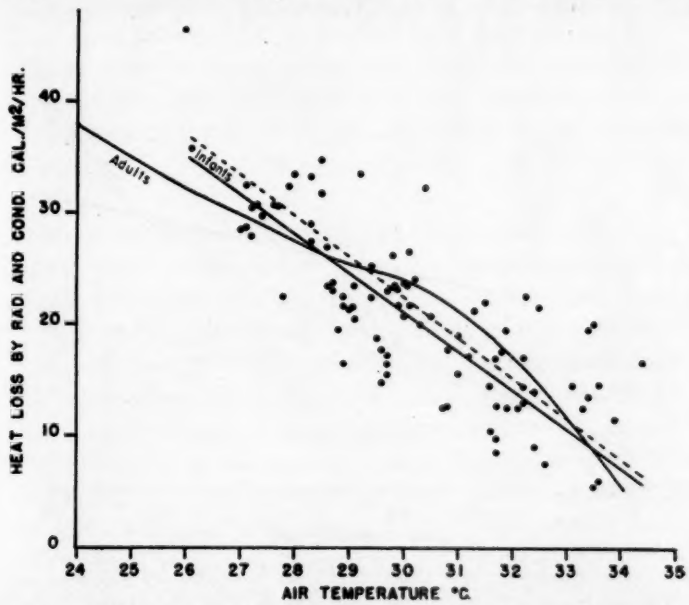

Chart 4.—The heat loss by radiation and conduction per square meter of body surface. The adult line was obtained by calculation from the data of Hardy and Soderstrom [7] and its downward deflection in warm air is probably the result of the cooling action on the skin of evaporation. The straight solid line is fitted to the data for the infants as explained in the text. The dotted line is the position the solid line would take if corrected for the possible systematic error discussed in the text.

and is doubtless the result of cooling of the skin by perspiration. The explanation of the other inflections is not clear. It is also possible that if only 1 or 2 infants had been studied many times (as was the case with the adults) the distribution of the points might not have been as linear as appears to be the case for the whole group of infants. The similarity in position of the curve for adults and the one for infants could in part be the result of greater losses by convection occurring under the condi-

tions of the adult experiments, which would compensate in part or entirely for the greater loss by radiation that would be expected of the infants from the fact that they had a higher average skin temperature (chart 8).

The similarity in slope of the curve for adults and the one for infants cannot be explained except by similarity of physiologic reactions to the varying air temperatures. There are, however, certain differences between them. In warm air most of the individual observations on the infants lie above the curve for adults, a fact most easily explained by the cooling effect of sweat on the adult skin. In cold air the individual observations on the infants also lie above the adult line. This could be in part the result of poor vasoconstriction or of the increased heat

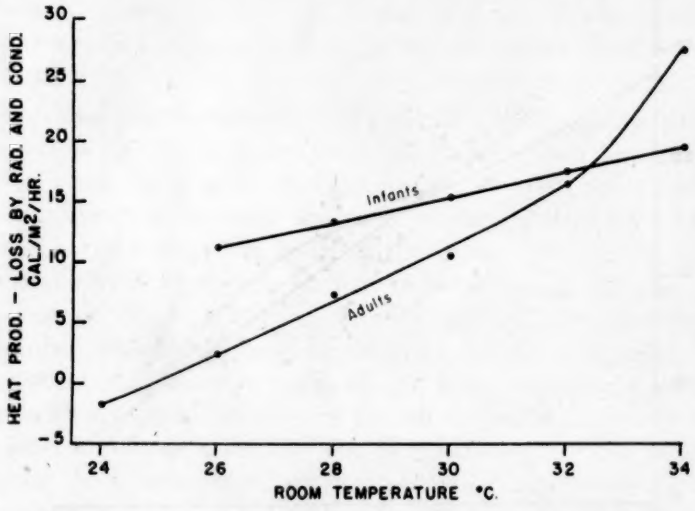

Chart 5.—The excess of heat production over heat loss by radiation and conduction. The adult curve is calculated from the data of Hardy and Soderstrom.[7] The more nearly horizontal the curve, the better the maintenance of a balance between heat loss by radiation and conduction and heat production. The apparent inferiority of the adults compared with the infants is the result of their voluntarily refraining from muscular activity in cool air and the cooling of their skin by sweating in warm air.

loss that would necessarily result from the increase in heat production in cool air previously shown to take place (chart 2). The adults, since they refrained from activity, had no such increase in heat production. Because of this difference in the two groups, a direct comparison of heat loss by radiation and conduction is not sufficient. A more suitable comparison consists in finding the difference between heat production and heat loss. The more constant this difference is in different environments, the more stable is the heat regulation of the subject. Such a

comparison is shown in chart 5. The curve for the infants indicates that a better balance is maintained by them than by adults. This surprising result is attained because of the elevated metabolism in cool air displayed by the infants. The curves of chart 5 strongly suggest that there is no defect in circulation in the infants sufficient to influence adversely the balance between heat production and heat loss as compared with adults. These curves do not, however, constitute proof of this point, since it is possible that the advantage of an elevated metabolism in cool air enjoyed by the infants obscures a defect in vasoconstriction. Consequently, a different method of analyzing the same data is presented in the following section.

Thermal Conductivity.—The efficiency of the circulatory reactions of premature infants can be studied by a method which involves the calculation of the thermal conductivity of the body. Burton,[5] Winslow, Herrington and Gagge[6] and Hardy and Soderstrom[7] have recently published data on adults in which they utilize the measurement of heat flow in order to calculate values for the rate of blood flow to the periphery.

Thermal conductance between the warm inner core of the body and the cooler skin surface depends on one fixed factor, the nature and thickness of the intervening body tissues, and on one variable factor, the rate at which the blood carries heat to the surface. Thus the transport of heat can be used to measure this variable factor, the circulation, much as the transport of carbon dioxide can be used to measure the cardiac output. Variations in conductance betoken variations in the blood brought to the surface, that is, in the peripheral circulation. Although one does not know the precise amount of blood represented by any given value for conductance, nevertheless changes in conductance provide a valid means of comparing qualitatively and to some extent quantitatively differences between the circulatory responses of two groups of subjects, such as infants and adults. In addition, if maximal vasoconstriction can be demonstrated in both groups (as we believe to be the case) at cool air temperatures, then values for conductance can be used to compare the differences between the two groups with regard to the fixed factor, the most important element of which is doubtless the thickness of the tissues, though their nature and the proportion of fat and skin also play a part. In short, one can measure the effectiveness of the insulating blanket with which the body is provided.

Conductance is equal to the total heat loss per hour per square meter of body surface per degree centigrade of difference between the temperature of the warm inner core (rectal temperature) and the temperature of the skin. The rationale of this equation becomes clear when one realizes that to maintain a large difference in temperature between

rectum and skin in the face of a large production of heat the insulating ability of the tissues must be good. Obversely, in order to lose an increased amount of heat, this heat must first be conducted out to the skin surface, and to do this the body raises the conductivity by increasing the rate of circulation. In any one instance, of course, the thickness of the body does not change.

Examination of this equation shows at once a conspicuous advantage of conductivity over skin temperature as a measure of circulation, because a value is provided which changes only when the circulation changes. Variations in heat production, air temperature and sweating cannot distort its value and, in fact, do not alter its value except by that very physiologic mechanism which we are interested in measuring, namely, the speed of the peripheral circulation.

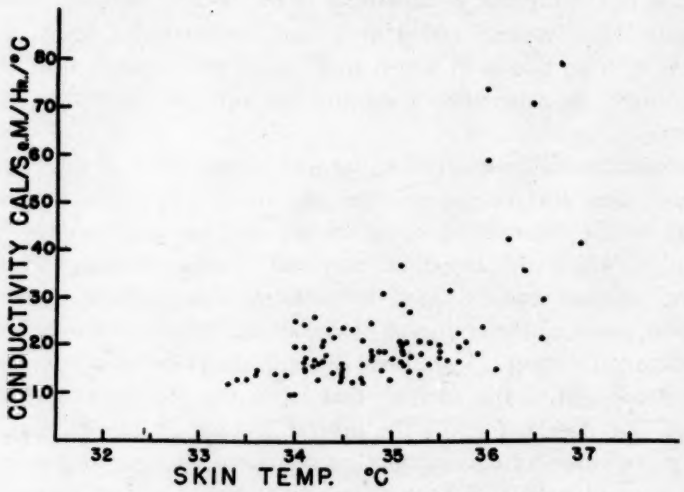

Chart 6.—Thermal conductance of the body at different air temperatures. As explained in the text, the increase in scatter in the warmer zone may be the result of experimental error and not of physiologic variability.

However, from a quantitative point of view, this index of circulation has a serious fault. In warm air the temperature of the skin becomes elevated and more closely approaches that of the rectum. Therefore, a given absolute error in either the rectal or the cutaneous temperature produces a progressively larger percentage error in the value for conductivity as one performs experiments in progressively warmer atmospheres. Since, as chart 8 shows, the skin temperature of premature infants is higher than that of adults, this fault is more serious in their case. Charts 6 and 7 show this greater scatter in the warmer zone.

Chart 6 shows all of the values for conductance that were determined. The values are shown at different levels of skin temperature. The

scatter is large and becomes larger in the warm zone for the reasons just given. It is of course possible that physiologic factors may also play a role in the increase in scatter in the warmer conditions, but such a conclusion is improbable because of the more likely part played by the factor of error.

For comparison of the results for adults with those for infants, the curves for adults from two different groups of workers are shown in chart 7. In order not to confuse the appearance of these curves with the multitude of points shown in chart 6, the values for infants in chart 7 are the arithmetical means of the values of chart 6 for all points falling within three different temperature zones. The standard devia-

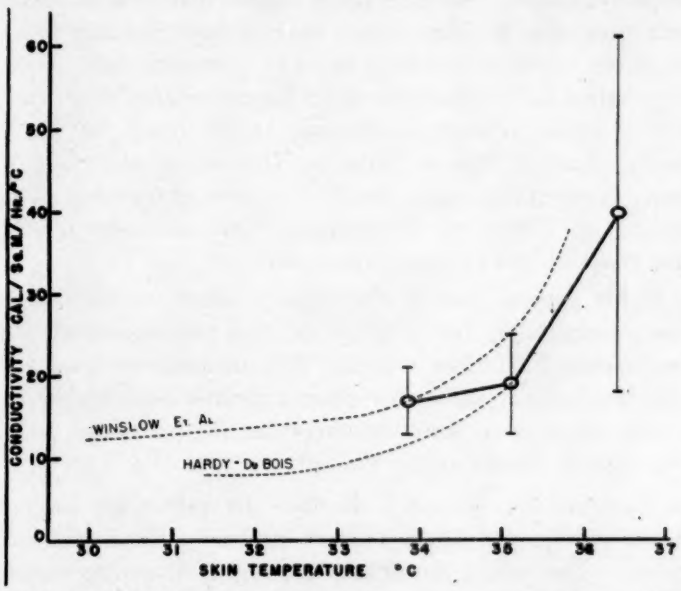

Chart 7.—Arithmetical mean of the data of chart 5 at three different levels of skin temperature. The vertical lines indicate the standard deviation of each value. The adult curves are indicated for comparison.

tions of these three means are also indicated. A more laborious statistical method of showing the average trend of the apparently curved distribution of points indicated in chart 6 and the apparently increased scatter in warm environments was not considered warranted by the nature of the data or the conclusions drawn from them.

All of the data for both adults and infants show that there is a rise in conductance associated with a rise in skin temperature. It is also clear that this rise is not linear, and thus a further defect in skin temperature as a measure of circulation is suggested. Since the curves for

both infants and adults rise when the skin temperature becomes elevated, it is fair to conclude that both groups of subjects have similar vascular reactions.

This method of analysis, then, does not indicate inferiority in the circulatory adjustments of premature infants as a group. The large amount of scatter, however, prevents one from making any statements about individual infants. It should further be borne in mind that all these infants were healthy and thriving at the time of observations.

What do the figures for thermal conductance show with reference to the comparative efficiency of the premature infant's protecting blanket of fatty tissues and skin? In general, it can be said that the conductance of premature infants is much higher than that of adults, and since their circulation has been shown to be reactive, it is fair to conclude that this is the result of a thinner layer of protecting fat. This elevation of the values for conductance of premature infants above the values for adults is more apparent in the case of the results of Hardy and Soderstrom [7] than in those of Winslow, Harrington and Gagge.[6] The discrepancy between the values obtained by these two groups of workers may depend on differences in method. Our methods more closely resembled those of Hardy and Soderstrom.[7]

The higher general level of conductance values for the infants is to some extent obscured in chart 7 by the fact that at any given air temperature a premature infant has a higher skin temperature than an adult. When the conductivity values are plotted against air temperature (not shown), the effect is to shift the curve for the premature infants, as shown in chart 7, somewhat to the left.

Skin Temperature.—Chart 8 displays the values for average skin temperature during each of the periods of observation as related to air temperature. The values for infants are higher than for adults. Not only is the line for adults in the figure lower than the apparent general average for the infants, but it flattens out in the warmer zones. This flattening is no doubt the result of the active perspiration that takes place in adults but not in premature infants. The periods in which the infants perspired are indicated by open circles. It may be asked why the infants who perspired did not have a slightly lower skin temperature as a result. The answer to this is obtained at once by noting the open circles in the graph of heat production (chart 2). It appears that not only did these infants perspire, but they had a greatly elevated heat production, a fact which would in itself tend to raise the skin temperature. The combined action of the cooling effect of the perspiration and the warming effect of the increased metabolism appear fortuitously to have just about neutralized each other.

Evaporative Loss.—So far as these data are concerned, most of the pertinent facts about evaporative loss have already been mentioned. Only a few of the infants perspired, and the chief defect in the ability of premature infants to maintain heat loss in warm air seems to lie in a defective output of sweat. So far as the general relation of evaporative loss to heat production or to air temperature or, in fact, to any other factor was concerned, little if any relationship could be shown to exist. The failure to detect a clearcut relation with heat production no doubt is a result of the facts that conditions were not basal and that the experimental error in measuring the extremely small quantities of water evaporated was large.

It would be interesting to inquire further as to whether the failure to sweat is a result of an immature regulating center in the brain or

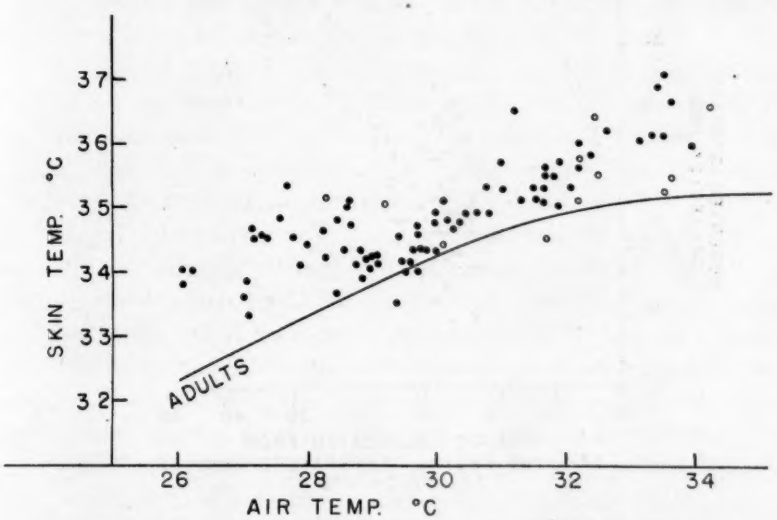

Chart 8.—Average skin temperatures at different levels of air temperature. The open circles indicate periods in which the infants perspired actively.

of inadequate sweat glands. The calorimetric data do not permit such an analysis. We have, however, begun work on an entirely different method, which involves heating the infant's body by placing the feet in warm water and noting under what circumstances sweating begins as detected by electrical methods. Preliminary results, which we hope to report later, indicate that the defect is in the amount of sweat produced and not in the failure of appropriate nervous impulses.

Storage of Heat.—Changes in cutaneous and rectal temperature may be used to calculate the amount of heat stored in or lost from the body. The proper weighting for each of these two measurements

may be arrived at statistically. To accomplish this a specific heat of 0.85 [7] was assumed for the body as a whole. The caloric equivalent of the rise or fall in cutaneous and in rectal temperatures was then calculated separately on the basis that each represented the true change of body temperature. These values were then compared with the values for heat storage obtained by noting the difference between the directly observed values for total heat production and total heat loss. The formula for the prediction of heat storage from cutaneous and rectal temperature thus statistically derived is as follows:

$$S = 2.77 + 0.43D + 0.68R$$

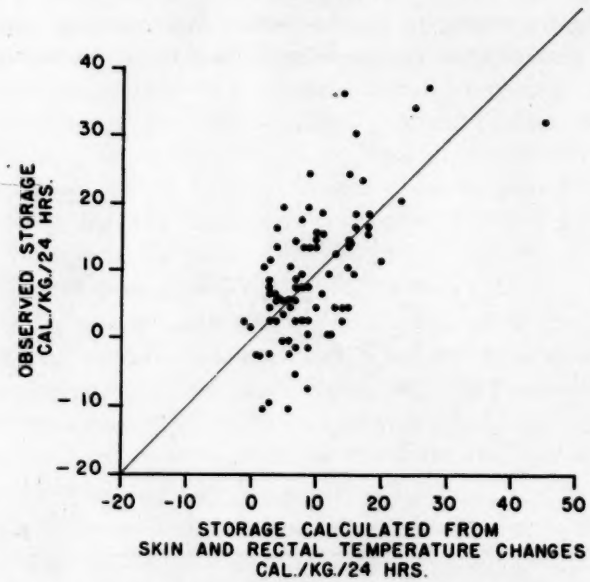

Chart 9.—The relationship of the observed storage of heat in the body and the storage calculated from cutaneous and rectal temperature as explained in the text. The scatter and the failure of the data to be distributed along the theoretic line of perfect agreement indicate the unreliability of short period estimations of average change of body temperature.

S is the number of calories stored per kilogram of body weight per twenty-four hours, and D and R are the number of calories stored per kilogram per twenty-four hours calculated from cutaneous and rectal temperatures alone, respectively. The factor 2.77 indicates that there is a systematic error somewhere in the observed data. It could be in the measurement of heat loss or of cutaneous temperature or of rectal temperature or in all three. It is the existence of this error which was referred to in the discussion of chart 4.

Chart 9 shows the comparison of observed and calculated values for storage. The coefficient of correlation of 0.66 ± 0.04 shows that the estimation of true change in premature infant's body temperature over short periods of time is difficult.

Other Factors.—In regard to all of these results and the discussions derived from them two additional facts must constantly be borne in mind. The first is that the surface area of a premature infant is large in proportion to body weight. For example, whereas a man weighing 75 Kg. has a surface area of 0.025 square meters per kilogram of weight, a premature infant weighing 2 Kg. has a surface area of 0.078 square meters per kilogram. Therefore, if the heat loss per unit area were the same for an adult and for an infant, the handicap of a large surface area would still exist. In comparison with full term infants Gordon and Levine [15] have shown that premature infants are at a considerable disadvantage in this respect.

The second point is that the premature infant has a feeble musculature. It has been shown [7] that for protection against cold vasoconstriction is a poor weapon both for the adult and for the premature infant, even if it is complete. The adults in the reports cited from the literature voluntarily refrained from muscular activity. Their heat production did not rise in cool air. The premature infants cried, and they had an elevation of heat production in cool air. However, there can be no doubt that a healthy adult or full term infant can exert much more muscular effort than can a premature infant, and for this reason the feeble musculature of the premature infant is an extremely important factor in his failure to prevent hypothermia. This idea receives considerable support from the work of Gordon and co-workers,[9] which shows that under conditions of normal activity during twenty-four hour periods full term infants have a metabolic rate 40 per cent above basal and premature infants show a rise of only 18 per cent.

It is also worthy of comment that most of the rectal temperatures in this study were below 37 C. (98.6 F.). The reactivity of the peripheral circulation as measured by thermal conductance was not influenced by the rectal temperature level. These two facts suggest but do not prove: (1) that the average rectal temperature of premature infants may actually be normally lower than the generally accepted values for children; and (2) that the skin seems to have a thermostatic control which is independent to a considerable extent of inner body temperature but is responsive to air temperature.

15. Gordon, H. H., and Levine, S. Z.: The Respiratory Metabolism in Infancy and in Childhood: XVIII. The Respiratory Exchange in Premature Infants—Basal Metabolism, Am. J. Dis. Child. **52**:810 (Oct.) 1936.

SUMMARY AND CONCLUSIONS

An evaluation has been made of the role of a number of factors contributing to the lability of body temperature of premature infants. By means of a calorimetric technic it has proved possible to make concurrent measurements on 25 healthy premature infants of heat production, heat loss by radiation and conduction, heat loss by evaporation, skin temperature and rectal temperature. In spite of technical difficulties sufficient accuracy was achieved to justify conclusions as to the characteristics of premature infants as a group.

The fact has been confirmed that in warm air the chief defect in the heat-regulating mechanism of the premature infant is an inadequacy of sweat production. Vasodilation takes place in a manner quantitatively similar to that of adults.

In cool air the total heat loss per unit area of skin appears to be greater than for adults. Factors contributing to this augmented heat loss are the greater thermal conductivity of the body tissues and an increased heat production in cold air. No defect in vasoconstriction was evident.

Cool air provokes an increase in heat production and also in the amount of crying. No definite statement can be made as to the presence or absence of so-called chemical regulation.

In cool air the chief handicaps from which the infant suffers are a large surface area in proportion to body weight and a feeble musculature; hence the sustained muscular movement necessary to raise heat production is more difficult for these feeble subjects than for adults.

Since most of these observations have been made on infants older than 1 week and weighing more than 2,000 Gm., the conclusions should not be extended without reserve to younger or smaller infants.

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EFFECTS OF VARIOUS URINARY ANTISEPTICS ON STRAINS OF ESCHERICHIA COLI

I. SULFATHIAZOLE

II. URINARY ACIDITY, MANDELIC ACID, METHENAMINE AND METHENAMINE MANDELATE

III. RELATIVE VALUE OF SULFATHIAZOLE, SULFADIAZINE, SULFAPYRIDINE, SULFACETIMIDE AND SULFANILAMIDE

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SULFATHIAZOLE

In former experiments I showed the great variations of the effect of sulfathiazole on twenty-one strains of Escherichia coli. Twenty more strains were added to this series, and the bactericidal action of sulfathiazole on these forty-one strains was tested. The results indicated a low resistance of most strains of Esch. coli to sulfathiazole. At a concentration of 2 mg. of sulfathiazole per hundred cubic centimeters of urine all but four strains were killed off in seventy-two hours (table 1). When the concentration of sulfathiazole was increased to 200 mg. per hundred cubic centimeters three of the four resistant strains were killed off at various higher levels. At the highest level, 200 mg. per hundred cubic centimeters, strain 22 still grew actively when it was inoculated in numbers of less than 100 bacilli per 0.5 cc. of urine.

In view of the great range of bactericidal effect, from a definite bactericidal effect on strain 13 at a concentration of 0.1 mg. of sulfathiazole per hundred cubic centimeters to rapid growth of strain 22 at a concentration of 200 mg. per hundred cubic centimeters, it appeared that it would be of value to determine in detail the bactericidal effect of various concentrations of sulfathiazole on four strains, two highly resistant strains (4 and 22) and two only slightly resistant or non-resistant strains (13 and 31).

In determining the effectiveness of the drug in urinary infections, my colleagues and I were interested particularly in determining the variation of the bactericidal action of the drug when the inoculum of bacteria is of various sizes. We diluted 0.1 cc. of a twenty-four hour brain broth culture with 9.9 cc. of urine and made counts of the number of bacteria in 0.5 cc. of urine. Our second dilution was also 1 in 100 and the third,

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fourth and fifth were 1 in 10. The bacterial counts of the five dilutions indicated more than 1,000,000 bacteria in dilution 1, more than 10,000 but less than 100,000 in dilution 2, more than 1,000 in dilution 3, more than 100 in dilution 4 and more than 10 in dilution 5.

The type of experiment carried out is illustrated in detail in table 2. Table 3 was selected because it showed the level at which a change in

TABLE 1.—*The Bactericidal Effect of Various Concentrations of Sulfathiazole on Forty-One Strains of Esch. Coli at* p_H *6.5*

Concentration of Sulfathiazole, Mg. per 100 Cc.	Number of Strains Killed Off as Indicated by Absence of Turbidity After 72 Hours	Number of Strains Not Killed Off as Indicated by Turbidity After 72 Hours
2	37	4
5	37	4
30	38	3
50	39	2
75	39	2
100	40	1

TABLE 2.—*The Growth of Strain 4 of Esch. Coli in Urine Containing 160 Mg. and 40 Mg. of Sulfathiazole per Hundred Cubic Centimeters*

Number of Bacteria in 0.5 Cc. of Urine		Bacterial Growth Indicated by Grade of Turbidity of Urine *		
Immediately After Inoculation	After 24 Hour Incubation	After 24 Hours	After 48 Hours	After 72 Hours
	160 Mg. per 100 Cc.			
1,600,000	Innumerable	3	3	3
16,000	111	0	0	0
1,240	5	0	0	0
113	0	0	0	0
19	0	0	0	0
	40 Mg. per 100 Cc.			
1,580,000	Innumerable	3	3	3
15,800	Innumerable	2	3	3
1,580	Innumerable	2	3	3
178	Innumerable	1	3	3
20	3,450	0	3	3

* Turbidity was graded 1 to 4; grade 4 represents greatest turbidity.

bactericidal action occurred with strain 13, the least resistant of the four strains. Most of the experiments carried out with strains 4, 13, 22 and 31 are summarized in table 4. Strain 22 grew out luxuriantly even when less than 100 bacilli per 0.5 cc were added to urine containing 200 mg. of sulfathiazole per hundred cubic centimeters (table 5).

Strain 4 (table 4) grew out in all five dilutions at 40 mg. of sulfathiazole per hundred cubic centimeters and was reduced in number only

in dilution 5 at 80 mg. per hundred cubic centimeters; it was killed off in all but dilution 1 at 160 mg. per hundred cubic centimeters (tables 2 and 4).

TABLE 3.—*The Growth of Strain 13 of Esch. Coli in Urine Containing 0.5 and 0.1 Mg. of Sulfathiazole per Hundred Cubic Centimeters*

Number of Bacteria in 0.5 Cc. of Urine		Bacterial Growth Indicated by Grade of Turbidity of Urine		
Immediately After Inoculation	After 24 Hour Incubation	After 24 Hours	After 48 Hours	After 72 Hours
	0.5 Mg. per 100 Cc.			
2,100,000	Innumerable	3	3	3*
21,000	490	0	0	0
2,100	64	0	0	0
205	0	0	0	0
20	0	0	0	0
	0.1 Mg. per 100 Cc.			
3,100,000	Innumerable	3	3	3
31,000	Innumerable	2	3	3
3,100	Innumerable	2	3	3
300	Innumerable	0	3	3
28	2	0	0	0

* Same turbidity picture at 160 mg. per hundred cubic centimeters.

TABLE 4.—*The Variations of the Effect of Sulfathiazole on Four Strains of Esch. Coli*

Strain	Dilution*	Bacterial Growth Indicated by Grade of Turbidity at Various Concentrations of Sulfathiazole, Mg. per 100 Cc.							
		160	80	40	1†	0.5	0.25	0.1	0.05
31.....	1	3	3	3	3	3	3	3	3
	2	0	2	1	1	2	1	3	3
	3	0	0	0	0	0	2	3	3
	4	0	0	0	0	0	0	3	3
	5	0	0	0	0	0	0	3	3
13.....	1	3	3	3	3	3	3	3	3
	2	0	0	0	0	0	1	3	3
	3	0	0	0	0	0	2	3	3
	4	0	0	0	0	0	0	3	3
	5	0	0	0	0	0	0	0	3
22.....	1	3	3	3					
	2	3	3	3					
	3	3	3	3					
	4	3	3	3					
	5	3	3	3					
4.....	1	3	3	3					
	2	0	3	3					
	3	0	3	3					
	4	0	3	3					
	5	0	0	3					

* Number of bacteria in 0.5 cc. of urine: 1 = more than 1,000,000; 2 = more than 10,000; 3 = more than 1,000; 4 = more than 100; 5 = more than 10.

† The concentrations of 20, 8, 4 and 2 mg. per hundred cubic centimeters show same growth pattern as 1 mg. per hundred cubic centimeters.

Strains 13 and 31 (table 4) resembled each other closely in their growth pattern, from 80 to 0.5 mg. of sulfathiazole per hundred cubic centimeters. With strain 31 there was a consistent slight growth in dilution 2, while with strain 13 there was growth in this dilution from 80

to 0.5 mg. per hundred cubic centimeters. At 0.25 mg. per hundred cubic centimeters with strains 31 and 13 there was growth after seventy-two hours in dilutions 1, 2 and 3, and at 0.1 mg. the number of bacteria of strain 13 was reduced only in dilution 5.

A striking feature of the summary of table 4 is the similarity of growth pattern for all concentrations of the drug when more than 1,000,000 bacteria per 0.5 cc. are added to the urine. No matter what the concentration of the drug, there was definite growth of all four strains in urine when the latter was inoculated with more than 1,000,000 bacilli per 0.5 cc. When one considers that at a concentration of 0.5 mg. of sulfathiazole per hundred cubic centimeters bacilli of strain 13 were killed off when the urine was inoculated with more than 10,000 but less than

TABLE 5.—*Bactericidal Effect of Sulfathiazole on Large Inoculations of Two Strains of Esch. Coli*

Strain	Concentration, Mg. per 100 Cc.	Number of Bacteria in 0.5 Cc. of Urine			
		Immediately After Inoculation	After 6 Hour Incubation	After 24 Hour Incubation	After 48 Hour Incubation
13	200	3,500,000	16,400,000	27,500,000	.....
	160	2,500,000	29,200,000	27,000,000	16,800,000
	5	3,500,000	40,700,000	50,000,000	.....
	200	350,000	206,000	3,000	90
	160	250,000	400,000	1,600	0
	5	350,000	2,710,000	13,700,000	.....
31	200	2,700,000	9,600,000	1,000,000	.....
	160	2,800,000	18,900,000	900,000	147,000
	5	2,700,000	47,000,000	70,000,000	.....
	200	270,000	251,000	3,000	390
	160	280,000	900,000	3,000	0
	5	270,000	5,850,000	34,800,000	.....
22 (control)	200	36	1,200	47,000,000	

100,000 bacilli per 0.5 cc. and grew out at 160 mg. of sulfathiazole per hundred cubic centimeters when more than 1,000,000 bacilli per 0.5 cc. were inoculated, then it becomes evident how large a role the size of the inoculum plays in a determination of bactericidal action.

To bridge the gap between the inoculation per 0.5 cc. of millions and of tens of thousands, an intermediate inoculation was used in experiments with strains 13 and 31, in which concentrations of 200, 160 and 5 mg. of sulfathiazole per hundred cubic centimeters of urine were used. Counts were taken after six and twenty-four hours and when indicated after forty-eight hours. Reference to table 5 shows that even at 200 and 160 mg. per hundred cubic centimeters when the urine contained more than 1,000,000 bacilli per 0.5 cc. rapid growth occurred for the first six hours and relatively little change occurred after this in the number of viable bacteria of each strain. At concentrations of 5 mg.

of sulfathiazole per hundred cubic centimeters, however, the numbers increased further after twenty-four hours when more than 1,000,000 bacteria per 0.5 cc. were added. When only a tenth of this number of bacilli, more than 100,000 per 0.5 cc., were added to the urine the number decreased slightly after six hours at 200 mg. of sulfathiazole per hundred cubic centimeters and increased at 160 and 5 mg. of sulfathiazole per hundred cubic centimeters after six hours; there was a great reduction in numbers after twenty-four hours at a concentration of 200 and 160 mg. but a further great increase of numbers at 5 mg. of sulfathiazole per hundred cubic centimeters after twenty-four hours. For comparison the growth of strain 22 is given to show how it increased from 36 bacilli in 0.5 cc. of urine immediately after inoculation to 1,200 after six hours and to 47,000,000 after twenty-four hours.

Comment.—A number of interesting deductions can be drawn from these experiments that concern the treatment of urinary infections.

The most striking deduction is perhaps that the maximal concentration of sulfathiazole at which different strains of Esch. coli resist its bactericidal action may vary from 0.1 mg. to more than 200 mg. per hundred cubic centimeters. Although the number of strains resistant to sulfathiazole is small, the resistance of the infecting strain may account for the failure of therapy in any particular case. Further, it is significant that when the number of bacilli in the urine is reduced to between 100 and 1,000 per 0.5 cc., 90 per cent of the strains will be killed off at a concentration of 2.5 mg. of sulfathiazole per hundred cubic centimeters.

As has been shown by Bigger and McNally,[1] Kohn and Harris [2] and others, sulfathiazole does not act bactericidally on bacteria immediately but for from six to nine hours there is a period in which multiplication of the bacteria is rapid and the organism is in the so-called logarithmic phase of growth. It is apparently in this phase of rapid multiplication that the bacteria become vulnerable to the action of sulfathiazole. As shown in table 5 and in many other of our experiments, this preliminary phase of multiplication precedes the phase of bactericidal action.

The second significant feature is the importance of the size of the inoculum of bacteria in the determination of bactericidal power. Definite bactericidal action occurred on strain 13 at a concentration of 0.1 mg. of sulfathiazole per hundred cubic centimeters when the urine contained less than 100 bacilli per 0.5 cc., but there was no bactericidal action on

1. Bigger, J. W., and McNally, P. A.: The Action of Certain Sulphonamide Drugs on the Growth of Bacteria in Urine, J. Path. & Bact. **52**:247-261 (March) 1941.

2. Kohn, H. I., and Harris, J. S.: On the Mode of Action of the Sulfonamides: I. Action on Escherichia Coli, J. Pharmacol. & Exper. Therap. **73**:343-361 (Nov.) 1941.

the same strain, even though the concentration of sulfathiazole was two thousand times as great, when the number of bacteria was more than 1,000,000 per 0.5 cc. of urine. This is of significance clinically in emphasizing the necessity of a reduction of the number of bacteria in the urine if urinary antiseptics are to exert their therapeutic action. It emphasizes the importance of diuresis and the difficulty of treating patients who have residual urine.

URINARY ACIDITY, MANDELIC ACID, METHENAMINE AND METHENAMINE MANDELATE

In the first portion of this paper I reported in detail the resistance of four strains of Esch. coli, two of which were resistant and two nonresistant to sulfathiazole, and in a previous publication my associates and I [3] have reported the effect of various urinary antiseptics on bacteria found in urinary infections resistant and nonresistant to sulfanilamide. In particular we were interested to see whether the resistance to other urinary antiseptics also applied to the two resistant strains 4 and 22, used in the study on sulfathiazole. As indicated in the title, we tried out four different procedures: antisepsis resulting from (1) acidity, (2) mandelic acid, (3) methenamine mandelate [4] and (4) methenamine.

Acidity.—Experiments were performed as shown in table 6 by using three dilutions of twenty-four hour bacterial cultures with inoculation ranges of more than 100,000, more than 1,000 and more than 100 bacilli per 0.5 cc. of urine with a p_H of 4.6, 4.4 and 4.2.

Evident at p_H 4.6 and 4.4 and most evident at p_H 4.2 were the resistance to acid of the two strains resistant to sulfathiazole and the lack of resistance to acid of the two strains nonresistant to sulfathiazole. In view of the proportionally greater number of strains nonresistant to sulfathiazole, seven other such strains and one additional strain resistant to sulfathiazole were tested for resistance to acidity. In no instance was the resistance of any of these additional strains comparable to that of the two resistant strains (4 and 22). The resistance of strains 4 and 22 was the same to acidity as to sulfathiazole, but the third strain resistant to sulfathiazole fell in the class of strains nonresistant to acidity.

Mandelic Acid.—In view of the fact that the bactericidal action of mandelic acid has been shown by Rosenheim to be due to the free, undissociated acid, it was to be expected that the results with this acid would

3. Helmholz, H. F.: Chemistry in Urinary Antisepsis, in Visscher, M. B.: Chemistry and Medicine, Minneapolis, University of Minnesota Press, 1940, pp. 212-222.

4. The methenamine mandelate used for this purpose was furnished by the Nepera Chemical Company, Inc., of Yonkers, New York.

parallel those with mere acidity of the urine, and such proved to be the case. As seen in table 7, strains 4 and 22 were resistant to 500 mg. of mandelic acid per hundred cubic centimeters of urine at p_H 5.48

TABLE 6.—*The Action of Normal Urine with a p_H of 4.2 on Strains of Esch. Coli Resistant and Nonresistant to Sulfathiazole*

Strains	Number of Bacteria in 0.5 Cc. of Urine		Growth of Bacteria Indicated by Grade of Turbidity		
	Immediately After Inoculation	After 24 Hour Incubation	After 24 Hours	After 48 Hours	After 72 Hours
4 (resistant).....	127,000	250,000	2	3	3
	1,270	1,670,000	2	3	3
	163	1,810,000	2	3	3
22 (resistant).....	186,000	1,390,000	2	3	3
	1,860	2,040,000	2	3	3
	132	3,890,000	2	3	3
13 (nonresistant).....	90,000	245	0	0	1
	900	20	0	0	0
	100	0	0	0	0
31 (nonresistant)*.....	143,000	12	0	0	0
	1,430	2	0	0	0
	193	0	0	0	0

* Seven strains nonresistant to and one resistant to sulfathiazole had the same growth pattern.

TABLE 7.—*The Action of Mandelic Acid in Concentrations of 500 Mg. per Hundred Cubic Centimeters of Urine at p_H 5.48 on Strains of Esch. Coli Resistant and Nonresistant to Sulfathiazole*

Strains	Number of Bacteria in 0.5 Cc. of Urine		Growth of Bacteria Indicated by Grade of Turbidity		
	Immediately After Inoculation	After 24 Hour Incubation	After 24 Hours	After 48 Hours	After 72 Hours
4 (resistant).....	116,000	Innumerable	3	3	3
	1,160	Innumerable	3	3	3
	155	Innumerable	3	3	3
22 (resistant).....	201,000	Innumerable	3	3	3
	2,010	Innumerable	3	3	3
	460	Innumerable	3	3	3
13 (nonresistant).....	69,000	49,100	±	±	±
	690	560	0	0	0
	71	89	0	0	0
31 (nonresistant)*.....	127,000	195,000	1	1	1
	1,270	860	0	0	0
	147	135	0	0	0

* Eight other nonresistant strains had same growth pattern.

and the nonresistant strains 13 and 31 were killed off at the same concentration of acid and p_H of the urine. Eight other nonresistant strains behaved in the same way as nonresistant strains 13 and 31 when inoculations were made between 100 and 1,000 bacilli per 0.5 cc.

Methenamine.—Although methenamine undoubtedly was the outstanding urinary antiseptic introduced before 1930, it has fallen rather

into obsolescence since the introduction of the host of new urinary antiseptics during the last twelve years. I decided to try out methenamine on the four strains at a concentration of 200 mg. per hundred cubic centimeters of urine and at p_H 6.5.

The results were surprising: As seen in table 8, there was an almost complete reversal of the bactericidal effect of this drug as compared with that of sulfathiazole. The two strains resistant to sulfathiazole and one of the nonresistant strains were killed off completely, even in the urine in which there were the greatest number of inoculated bacilli. Strain 31 grew out to innumerable bacilli in the two highest dilutions used within twenty-four hours. Eight other strains nonresistant to sulfathiazole grew

TABLE 8.—*The Action of Methenamine in Concentration of 200 Mg. per Hundred Cubic Centimeters of Urine at p_H 6.5 on Strains of Esch. Coli Resistant and Nonresistant to Sulfathiazole*

Strains	Number of Bacteria in 0.5 Cc. of Urine		Growth of Bacteria Indicated by Grade of Turbidity		
	Immediately After Inoculation	After 24 Hour Incubation	After 24 Hours	After 48 Hours	After 72 Hours
4 (resistant).....	146,000	10	0	0	0
	1,460	0	0	0	0
	199	0	0	0	0
22 (resistant).....	130,000	7,920	0	0	±
	1,300	0	0	0	0
	173	0	0	0	0
13 (nonresistant).....	139,000	5	0	0	0
	1,390	1	0	0	0
	198	0	0	0	0
31 (nonresistant)*.....	168,000	Innumerable	2	2	3
	1,680	Innumerable	1	2	3
	216	10,800	0	2	3

* Eight other nonresistant strains had the same growth pattern.

out just as did strain 31 when inoculations were made with between 100 and 1,000 bacilli per 0.5 cc. of urine. The two strains resistant to sulfathiazole are thus nonresistant to methenamine, and nine of ten strains that are nonresistant to sulfathiazole are resistant to methenamine.

Methenamine Mandelate.—In view of the special attributes assigned to the recently introduced methenamine mandelate, a combination of mandelic acid and methenamine, I decided to see what effect this drug would have on the four strains of Esch. coli. In order to compare its bactericidal action with the action of its two components, mandelic acid and methenamine, it seemed logical to study its effect in the lowest concentration and at the highest p_H at which one of the component drugs acted bactericidally. Methenamine acted bactericidally at 200 mg. per hundred cubic centimeters of urine at p_H 6.49. I therefore used the same concentration of methenamine mandelate and the same p_H of the urine. As will be seen in table 9, the result was not as good as

with the same concentration of methenamine; nevertheless, the effect of methenamine mandelate paralleled closely the effect of methenamine. Resistant strains 4 and 22 and nonresistant strain 13 were killed off in dilutions 2 and 3, but all three strains grew out in dilution 1. Strain 31 and eight other strains nonresistant to sulfathiazole grew out to innumerable organisms in twenty-four hours when between 100 and 1,000 bacilli were inoculated per 0.5 cc. of urine.

Comment.—Resistance of a specific strain to one urinary antiseptic does not indicate a similar quality to another antiseptic.

Strains 4 and 22, resistant to sulfathiazole, were also resistant to mandelic acid and to acidity of the urine. Resistance to sulfathiazole,

TABLE 9.—*The Action of Methenamine Mandelate in Concentration of 200 Mg. per Hundred Cubic Centimeters of Urine at p_H 6.49 on Strains of Esch. Coli Resistant and Nonresistant to Sulfathiazole*

Strains	Number of Bacteria in 0.5 Cc. of Urine		Growth of Bacteria Indicated by Grade of Turbidity		
	Immediately After Inoculation	After 24 Hour Incubation	After 24 Hours	After 48 Hours	After 72 Hours
4 (resistant).....	148,000	60,000,000	2	3	3
	1,480	10,600	0	1	2
	154	1	0	0	0
22 (resistant).....	277,000	34,000,000	2	3	3
	2,770	100	0	0	0
	400	20	0	0	0
13 (nonresistant).....	94,000	10,000	1	1	2
	940	95	0	0	0
	104	1	0	0	0
31 (nonresistant)*.....	146,000	23,000,000	3	3	3
	1,460	46,000,000	3	3	3
	208	33,000,000	3	3	3

* Eight other nonresistant strains had the same growth pattern.

mandelic acid and acidity, on the one hand, was associated in strains 4 and 22 with great susceptibility to methenamine and methenamine mandelate, on the other. Strain 13, most susceptible to sulfathiazole, was extremely susceptible to the action of the other four antiseptics. Strain 31, nonresistant to sulfathiazole, acidity and mandelic acid, was resistant to methenamine mandelate and methenamine. Eight other strains nonresistant to sulfathiazole showed the same resistance to methenamine and methenamine mandelate.

The specific resistance of different strains of the same bacterium becomes for the clinician a definite problem in the treatment of urinary infections. It thus becomes necessary to know not only what the infecting bacterium is but whether it is resistant or susceptible to a particular urinary antiseptic; perhaps it is better to know to which

urinary antiseptic it is most susceptible. If at the time that cultures are taken of the urine a loopful of the infected urine is added to comparable concentrations of three or four urinary antiseptics, after twenty-four hours' incubation it should be possible to say with some degree of certainty which of the four is most likely to give a successful therapeutic result. Studies are now under way to determine such standards.

RELATIVE VALUE OF SULFATHIAZOLE, SULFADIAZINE, SULFAPYRIDINE, SULFACETIMIDE AND SULFANILAMIDE

The differences in bactericidal action of the various drugs on the four strains of Esch. coli made it seem of interest to compare the bactericidal action of five of the well known sulfonamide compounds, sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine and sulfacetimide on these four strains.

Each of the five sulfonamide compounds was administered by mouth to normal persons for a period of two days. The urine collected was sterilized by passage through Berkefeld filters and was diluted to the proper concentration with sterile normal urine.

The bacterial inoculations of urine were made in the same way as in former experiments. Five dilutions of a twenty-four hour broth culture were used. These resulted in bacterial counts of more than 1,000,000, more than 10,000, more than 1,000, more than 100 and more than 10 bacteria per 0.5 cc. of urine. Bacterial counts were made after incubation for five and twenty-four hours, and turbidity readings were made after incubation for five, twenty-four, forty-eight and seventy-two hours. In some of the experiments the urine contained from 1,000 to 10,000 bacteria per 0.5 cc., as shown in table 10. In this table are given both the bacterial counts and the turbidity results in a study of the action of sulfacetimide. An increase in the number of bacteria was seen after incubation for five hours in most instances, and a significant reduction was seen after twenty-four hours whenever there was any bactericidal effect. In tests on strain 13, which was the least resistant strain, the number of bacteria did not increase after five hours' incubation.

The results of the experiments with strains 4, 13, 22 and 31 are given in table 11. With concentrations of 1, 10 and 80 mg. per hundred cubic centimeters only the 80 mg. of sulfadiazine exerted a bactericidal effect on strain 4. None of the compounds exerted a bactericidal or bacteriostatic effect on strain 22.

Strains 13 and 31 showed growth in concentrations of 1 and 10 mg. of sulfanilamide and 1 mg. of sulfacetimide and sulfapyridine per hundred cubic centimeters and were killed by a concentration of 1 mg. of sulfathiazole and sulfadiazine per hundred cubic centimeters. A single set of experiments with sulfapyrazine showed growth at a concentration

of 80 mg. per hundred cubic centimeters of strains 4, 22 and 31 and a bactericidal effect on strain 13 only.

The close resemblance of the results obtained with sulfathiazole and sulfadiazine made it significant to test out the resistance of the entire

TABLE 10.—*The Bactericidal Effect of Various Concentrations of Sulfacetimide on Four Strains of Esch. Coli*

Strain	Number of Bacteria in 0.5 Cc.			Growth of Bacteria Indicated by Grade of Turbidity		
	Immediately After Inoculation	After Incubation of		After 24 Hours	After 48 Hours	After 72 Hours
		5 Hours	24 Hours			
			80 Mg. per 100 Cc.			
4	1,410	14,900	75,000,000	3	3	3
13	1,490	400	0	0	0	0
22	2,460	112,000	112,000,000	3	3	3
31	1,910	21,000	0	0	0	0
Control	0	0	0	0	0	0
			10 Mg. per 100 Cc.			
4	3,810	39,000	119,000,000	3	3	3
13	1,880	6,400	100	0	0	0
22	5,800	113,000	56,000,000	3	3	3
31	2,890	25,000	90	0	0	0
Control	0	0	0	0	0	0
			1 Mg. per 100 Cc.			
4	2,920	108,000	137,000,000	3	3	3
13	1,820	9,500	116,000	1	2	2
22	6,300	214,000	10,000,000	3	3	3
31	2,370	34,000	279,000	1	2	2
Control	0	0	0	0	0	0

TABLE 11.—*A Comparison of the Bactericidal Action of Five Sulfonamide Compounds* on Four Strains of Esch. Coli*

Strain	Bacterial Growth as Evidenced by Grade of Turbidity After 72 Hours' Incubation														
	Sulfanilamide, Mg. per 100 Cc.			Sulfathiazole, Mg. per 100 Cc.			Sulfadiazine, Mg. per 100 Cc.			Sulfacetimide, Mg. per 100 Cc.			Sulfapyridine, Mg. per 100 Cc.		
	1	10	80	1	10	80	1	10	80	1	10	80	1	10	80
4 (resistant)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
22 (resistant)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
13 (nonresistant)	3	3	0	0	0	0	0	0	0	3	0	0	3	0	0
31 (nonresistant)	3	1	0	0	0	0	0	0	0	2	0	0	2	0	0

* Sulfapyrazine: growth 3 for strains 4, 22 and 31 at 80 mg. per hundred cubic centimeters; no growth for strain 13 at 80 mg. per hundred cubic centimeters.

group of strains of Esch. coli to each of the sulfonamide compounds except sulfanilamide, which was far behind the others in effectiveness. Since concentrations of 1 mg. of these drugs have been used in the experiments with the four organisms, I decided to use slightly higher and slightly lower concentrations. One series of experiments was carried

out in which the concentration of each one of the four sulfonamide compounds was 2 mg. per hundred cubic centimeters of urine and another series of experiments in which a concentration of 0.5 mg. per hundred cubic centimeters was used. In these experiments thirty-eight strains of Esch. coli were inoculated into specimens of urine containing 2 mg. and 0.5 mg. per hundred cubic centimeters of each of the four sulfonamide compounds except sulfanilamide. Between 1,000 and 10,000 organisms per 0.5 cc. of the urine were present after inoculation.

TABLE 12.—*A Comparison of the Bactericidal Effect of 2 Mg. of Sulfathiazole, Sulfadiazine, Sulfacetimide and Sulfapyridine per Hundred Cubic Centimeters of Urine on 38 Strains of Esch. Coli*

	Number of Tubes Showing Bacterial Growth as Indicated by Turbidity of Urine		
	After 24 Hours	After 48 Hours	After 72 Hours
Sulfathiazole	0	1	3
Sulfadiazine	2	3	4
Sulfacetimide	30	35	35
Sulfapyridine	36	37	37

TABLE 13.—*A Comparison of the Bactericidal Effect of 0.5 Mg. of Sulfathiazole, Sulfadiazine, Sulfacetimide and Sulfapyridine per Hundred Cubic Centimeters of Urine on 38 Strains of Esch. Coli*

	Number of Tubes Showing Bacterial Growth as Indicated by Turbidity of Urine		
	After 24 Hours	After 48 Hours	After 72 Hours
Sulfathiazole	1	5	9
Sulfadiazine	23	29	30
Sulfacetimide	38	38	38
Sulfapyridine	37	37	37

The results of the urinary concentration of each of the sulfonamide compounds of 2 mg. per hundred cubic centimeters are given in table 12. As in the previous experiments with the four strains the effects of sulfathiazole and sulfadiazine were practically the same and those of sulfacetimide and of sulfapyridine were practically alike; the former two drugs permitted bacterial growth in only three and four of the thirty-eight strains respectively and the latter two in thirty-five and thirty-seven of the thirty-eight strains.

The results of experiments in which a concentration of 0.5 mg. of each of these four sulfonamide compounds per hundred cubic centimeters of urine was used are given in table 13. The results obtained with sulfathiazole and sulfadiazine in this concentration were decidedly different.

Of thirty-eight strains inoculated, only nine grew out in the urine containing sulfathiazole and thirty grew out in the urine containing sulfadiazine. Sulfacetimide did not inhibit growth of any strain, and sulfapyridine inhibited the growth of only one of the thirty-eight strains.

Analyzing the experiments with the four strains and the thirty-eight strains of Esch. coli, there can be no doubt that to destroy these organisms sulfathiazole and sulfadiazine are superior to sulfacetimide and sulfapyridine, and the latter two are superior to sulfanilamide. The effect exerted by sulfathiazole and sulfadiazine was essentially the same at the higher concentrations, but at a concentration of only 0.5 mg. per hundred cubic centimeters sulfathiazole was definitely superior to sulfadiazine in the bactericidal action on Esch. coli.

CONCLUSIONS

Resistance to sulfathiazole is manifested by a small percentage of strains of Esch. coli.

The size of the inoculum of bacteria may determine the presence or absence of bactericidal action.

Strains resistant to sulfathiazole were also resistant to urinary acidity and mandelic acid but were more susceptible to methenamine and methenamine mandelate than nonresistant strains.

Sulfathiazole and sulfadiazine seem to be more effective against Esch. coli than sulfacetimide, sulfapyridine or sulfanilamide. In concentrations of 0.5 mg. per hundred cubic centimeters sulfathiazole is more effective than sulfadiazine.

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CALCIUM AND PHOSPHORUS REQUIREMENTS OF PREMATURE INFANTS

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An important determinant of the calcium and phosphorus requirements of premature infants is the fact that premature birth has deprived them of placental nutrition for a period during which they would normally have acquired the major portion of their stores of these minerals.[1] This factor may also be expected to influence postnatal retention of minerals by premature infants. The observations to be reported consist of studies of the calcium and phosphorus metabolism of 5 prematurely born infants fed at low and at high levels of mineral intake (human and cow's milk respectively). On the basis of data in the literature on the chemical composition of the fetus at different ages and the mineral retentions of full term infants, standards of retention have been formulated as a guide to dietary requirements. Since the subjects all received large amounts of vitamin D, the data permit a more satisfactory assessment of the relative merits of the two diets than could be made from previous studies.[2]

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2. (*a*) Hamilton, B.: Calcium and Phosphorus Metabolism of Prematurely Born Infants, Acta pædiat. **3**:1, 1922. (*b*) Hamilton, B., and Moriarty, M.: The Composition of Growth in Infancy: I. A Premature Infant, Am. J. Dis. Child. **37**:1169 (June) 1929. (*c*) Muhl, G.: The Fat Absorption and the Calcium Metabolism of Prematurely Born Infants, Acta pædiat. **5**:188, 1926. (*d*) Paffrath, H., and Massart, J.: Langfristige Untersuchungen des Mineral- und Wasserstoffwechsels bei Frühgeborenen, Ztschr. f. Kinderh. **54**:343, 1932.

EXPERIMENTAL PROCEDURE AND METHODS

Subjects and Diets.—Five healthy prematurely born male infants were studied for periods varying from three to twenty-four days each. Their nutritional status and diets are given in table 1; data on their energy and water exchange have already been reported.[3] The human milk diets consisted of frozen, pooled mothers' milk, boiled for five minutes prior to use. The cow's milk diets consisted of a powdered skimmed milk–olive oil preparation (olac) diluted with water and, in the case of 1 infant (L. O.), fortified with additional dextrimaltose. One infant, E. C., was studied both with human and with cow's milk feedings. Foreperiods of at least four days with the same diet preceded the periods of collection of urine and feces. Each infant received 20 drops daily of percomorph liver oil (a concentrated source of vitamins A and D), this dose containing approximately 4,000 U. S. P. units of vitamin D.

Methods.—The technic of measuring the amount of food actually ingested and retained has been described.[3] Urine and feces were collected separately, and analysis was made on specimens pooled for periods of at least three days. The following methods were employed in triplicate for analyses of the diet, urine and feces: the McCrudden[4] method for calcium; the Tisdall[5] method for phosphorus and a modification of the Briggs[6] method for magnesium, the magnesium being precipitated according to the technic of Godden and Duckworth[7] and the final colorimetric determinations of phosphorus being made by the Fiske and Subbarow[8] method; the macro-Kjeldahl method for nitrogen, and the Roese-Gottlieb method for fat.[9]

RESULTS

The results are presented in table 2. They support the conclusions of Paffrath and Massart[2d] that for the prematurely born infant as for

3. (*a*) Gordon, H. H.; Levine, S. Z.; Deamer, W. C., and McNamara, H.: Respiratory Metabolism in Infancy and in Childhood: XXIII. Daily Energy Requirements of Premature Infants, Am. J. Dis. Child. **59**:1185 (June) 1940. (*b*) Gordon, H. H.; Levine, S. Z.; McNamara, H.; Marples, E., and Benjamin, H. R.: Respiratory Metabolism in Infancy and in Childhood: XXIV. Daily Water Exchange of Premature Infants, ibid. **61**:524 (March) 1941.

4. McCrudden, F. H.: The Determination of Calcium in the Presence of Magnesium and Phosphates: The Determination of Calcium in Urine, J. Biol. Chem. **10**:187, 1911-1912.

5. Tisdall, F. F.: A Rapid Colorimetric Method for the Quantitative Determination of the Inorganic Phosphorus in Small Amounts of Serum, J. Biol. Chem. **50**:329, 1922.

6. Briggs, A. P.: A Colorimetric Method for the Determination of Small Amounts of Magnesium, J. Biol. Chem. **52**:349, 1922.

7. Godden, W., and Duckworth, J.: Variations in Serum-Magnesium and in the Partition of Serum-Calcium in Normal Parturition and in Milk Fever, Biochem. J. **29**:445, 1935.

8. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

9. Roese-Gottlieb, in Official and Tentative Methods of Analysis, Washington, D. C., Association of Official Agricultural Chemists, 1925, pt. 19, p. 262.

TABLE 1.—*The Nutritional Status and Average Daily Diet of Subjects*

Subject	Birth Weight, Gm.	Duration of Observation, Days	Age, Days		Height, Cm., Initial	Weight, Gm.				Average Daily Diet		
			Initial	Final		Initial	Final	Average	Daily Gain	Milk, Gm. Human	Milk, Gm. Cow's *	Water, Gm.
E. C.	2,170	3	13	16	45.5	2,048	2,114	2,081	22	354	..	...
R. L.	1,200	3	41	44	41.5	1,578	1,639	1,608	20	314	..	...
M. B.	1,500	24	18	47	42.0	1,716	2,586	2,071	31	441	..	...
L. O.	1,960	18	31	74	46.0	2,366	4,127	3,143	43	...	63†	467
H. L.	1,920	10	23	38	47.0	2,564	2,927	2,578	27	...	76	309
E. C.	2,170	8	20	28	47.5	2,417	2,727	2,720	41	...	67	272

* A powdered, skimmed milk-olive oil preparation (olac) was used.
† Twenty grams of dextrimaltose was added daily to this feeding mixture.

TABLE 2.—*Mineral Balances in Terms of Twenty-Four Hours*

Milk	Subject	Period of Study, Days	Calcium					Phosphorus						Fat		Nitrogen		Magnesium		
			Intake, Mg./Kg.	Retention			Output Ratio, Urinary/Fecal	Intake, Mg./Kg.	Retention				Output Ratio, Urinary/Fecal	Retention Ratio, Ca/P	Intake, Gm./Kg.	Fecal Excretion/Intake, %	Intake, Mg./Kg.	Retention, Mg./Kg.	Intake, Mg./Kg.	Retention	
				Mg./Kg.	Weight Gain, Gm./Kg.	% of Intake			Mg./Kg.	Theoretic § Mg./Kg.	Weight Gain, Gm./Kg.	% of Intake								Mg./Kg.	% of Intake
Human	M. B.	24	57.8	29.3	1.94	51	0.23	28.9	25.0	27.4	1.73	87	2.1	1.2	8.0	31	361	222	12.4	5.8	47
	E. C.	3	47.5	15.5	1.47	33	0.36	23.6	21.4	17.0	2.03	91	‖	0.7	7.6	14	304	162	11.1	2.5	23
	R. L.	3	52.2	20.0	1.57	38	0.17	23.9	20.0	22.1	1.61	84	0.8	1.0	8.2	21	339	211	....	...	..
Average *			56.4	27.0	1.86	45	0.23	27.9	24.1 †	25.8	1.75	87	1.8	1.1	8.0	28	353	214	12.2	5.4	44
Cow's	L. O.	18	138.9	110.4	8.55	80	0.06	90.6	63.1	72.4	4.82	70	2.6	1.8	3.8	20	694	299	34.5	27.7	80
	E. C.	8	186.8	102.6	6.35	55	0.16	127.1	66.7	69.8	4.22	52	0.8	1.5	4.8	16	961	322	43.6	33.8	77
	H. L.	10	193.6	130.8	13.29	67	0.14	126.1	65.0	83.8	6.63	51	2.9	2.0	5.3	41	965	321	48.1	41.3	86
Average *			164.6	114.1	9.36	71	0.10	108.6	63.4 ‡	74.8	5.18	61	2.3	1.8	4.4	25	831	310	39.1	32.8	81

* Averages are weighted for days.
† Average is 93% of the theoretic phosphorus retention.
‡ Average is 85% of the theoretic phosphorus retention.
§ Calculated according to the formula: $P \text{ retained} = \frac{Ca \text{ retained}}{2} + \frac{N \text{ retained}}{17.4}$ [29].
‖ Urinary P was too low to be accurately determined.

the full term infant [10] the amount of calcium retained varies in general with the dietary supply. Thus a daily average intake of calcium from the human milk diet of 56 mg. per kilogram resulted in a retention of 27 mg., whereas the higher intake (165 mg.) in cow's milk was associated with an average retention of 114 mg. Surprisingly, the average percentage retention with cow's milk feedings of 71 per cent, with a range of from 55 to 80 per cent, was higher than the corresponding values of 45 per cent, with a range of from 33 to 51 per cent, with human milk feedings. Thus, 80 per cent of the increment of 109 mg. of calcium was retained. The significance of this rise in efficiency of utilization with increased intake will be discussed later.

Retention of phosphorus similarly showed a direct relationship to dietary supply: A daily average intake of 28 mg. per kilogram from human milk permitted a retention of 24 mg. per kilogram, and an intake of 109 mg. from cow's milk resulted in a retention of 63 mg. The fraction of dietary phosphorus retained was 87 per cent from the human milk, with a range of from 84 to 91 per cent, and 61 per cent from the cow's milk diet, with a range of from 51 to 70 per cent.

The higher intake of magnesium in the cow's milk preparation (39 mg. per kilogram as compared with 12 mg. per kilogram in the human milk) resulted in an absolute retention of 33 mg., as compared with 5 mg. retained from human milk. The increase in percentage retention from 44 to 81 per cent with the increase in absolute intake of magnesium parallels the results with respect to calcium.

Comparison of these results with those previously reported [2] for premature infants receiving no antirachitic supplements shows expected differences. Thus the percentages of dietary calcium and phosphorus retained by this series of infants were greater and the variability was less than those reported in the literature.[11] The single exception was the study of Muhl,[2c] in which premature infants fed human milk without added vitamin D showed calcium retentions as high as those here observed with human milk plus vitamin D.

There is a dearth of data for young full term infants fed human milk plus vitamin D which might serve as a basis for comparison with the results obtained in this study on premature infants. With a diet of cow's milk plus vitamin D, however, the average percentage retentions by two groups of young full term infants [12] were only 30 per cent for

10. Rominger, E., and Meyer, H.: Mineralstoffwechseluntersuchungen beim Säugling: I. Die Salzretention des gesunden Brust- und Flaschenkindes, Arch. f. Kinderh. **80**:195, 1927.

11. Hamilton.[2a] Hamilton and Moriarty.[2b] Paffrath and Massart.[2d]

12. (*a*) Jeans, P. C.; Stearns, G.; McKinley, J. B.; Goff, E. A., and Stinger, D.: Factors Possibly Influencing the Retention of Calcium, Phosphorus and Nitro-

(Footnote continued on next page)

calcium and 27 per cent for phosphorus, as compared with 71 and 61 per cent, respectively, for the prematurely born infants in this study.

COMMENT

Premature infants present no defect in ability to retain calcium and phosphorus, for they retain more when they are given more, and they retain proportionately more than do full term infants with a similar diet, e. g., cow's milk plus vitamin D. The tendency to osteoporosis [13] and to rickets, to the extent that osteoporosis may contribute to rickets, cannot then be attributed to a defect in ability to retain calcium or phosphorus.

Three questions arise for discussion: 1. Why was the calcium of cow's milk more fully retained than that of human milk? 2. What is the cause of the increased efficiency in calcium retention of premature infants when compared with full term infants? 3. How well do human or cow's milk feedings satisfy the requirements of premature infants?

1. Why Was the Calcium of the Cow's Milk Preparation More Fully Retained than That of Human Milk?

In rapidly growing infants the proportion of retained calcium to phosphorus is between 1.5:1 and 2:1.[14] Since the human milk used in this study had a calcium to phosphorus ratio of 2.1 and the cow's milk a ratio of 1.5, proper retention ratios could have resulted only from retention of similar percentages of both minerals. Actually this occurred with cow's milk, the average percentages being 71 and 61 per cent and the calcium to phosphorus ratio 1.8. With human milk, however, virtually maximum retentions of phosphorus (84 to 91 per cent of the intake) were accompanied by much lower retentions of calcium (33 to 51 per cent). The resultant low ratios of calcium to phosphorus, of 0.7 to 1.2, denote relatively poor calcification.[14] The high percentage retention of phosphorus from human milk precludes considering inefficient phosphorus retention as the cause of this poor calcification. Actually, retention of 100 per cent of the phosphorus of human milk with utilization of all the additional phosphorus for formation of bone would have permitted a retention of only 53 per cent of the calcium intake and a retention ratio of only 1.1. The paradoxic finding that

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gen by Infants Given Whole Milk Feedings: I. The Curding Agent, J. Pediat. **8**:403, 1936. (*b*) Daniels, A. L.; Stearns, G., and Hutton, M. K.: Calcium and Phosphorus Metabolism in Artificially Fed Infants: I. Influence of Cod Liver Oil and Irradiated Milk, Am. J. Dis. Child. **37**:296 (Feb.) 1929.

13. (*a*) Ylppö, A.: Das Wachstum der Frühgeborenen von der Geburt bis zum Schulalter, Ztschr. f. Kinderh. **24**:111, 1919. (*b*) Hess, A. F.: Rickets, Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1935.

14. Stearns, G.: The Significance of the Retention Ratio of Calcium: Phosphorus in Infants and in Children, Am. J. Dis. Child. **42**:749 (Oct., pt. 1) 1931.

infants receiving a smaller amount of calcium in the form of human milk retain a smaller fraction of it than those given a larger amount in the form of cow's milk can be explained by the limited total dietary supply of phosphorus, part of which is preferentially used for building up of protoplasm rather than for skeletal calcification. To increase calcium retention from human milk, the addition of phosphorus as well as of calcium would be necessary. An opportunity to test this point was not available.

2. What Are the Causes of the Increased Efficiency in Calcium Retention of Premature Infants when Compared with Full Term Infants?

Important factors which influence retention of calcium are: (A) efficiency of absorption of fat and vitamin D from the intestinal tract; (B) rate of body growth; (C) activity of the parathyroid glands, and (D) previous degree of mineral saturation of the bones. (The present report contains no data which would permit evaluation of peculiarities of metabolism of dietary acid-base [15] or lactose [16] in premature infants if such peculiarities exist. Furthermore, no estimate can be made concerning differences in availability of dietary phosphorus.)

Of these factors, the first two, as will be shown later, might be expected to diminish rather than increase retention of calcium. The data suggest that the third factor is not responsible, and it therefore appears that the previous desaturation of their bones is the most likely factor leading to greater efficiency of mineral retention of premature infants when compared with full term infants. The reasons for this conclusion will be discussed in the following paragraphs.

A. Absorption of Fat: Since premature infants excrete more fat than full term infants,[17] a parallel increase in fecal excretion of calcium resulting from increased intestinal formation of calcium soaps would be expected to diminish retention of calcium. The premature infants in the present study excreted fecal fat ranging from 14 per cent to as much as 41 per cent of the ingested fat, but even in those infants whose excre-

15. Shohl, A. T.: The Effect of the Acid-Base Content of the Diet upon the Production and Cure of Rickets with Special Reference to Citrates, J. Nutrition **14**:69, 1937.

16. French, R. B., and Cowgill, G. R.: Immaturity of the Organism as a Factor Determining the Favorable Influence of Lactose on the Utilization of Calcium and Phosphorus, J. Nutrition **14**:383, 1937.

17. (*a*) Rubner, M., and Langstein, L.: Energie- und Stoffwechsel zweier frühgeborener Säuglinge, Arch. f. Physiol., 1915, p. 39. (*b*) Tidwell, H. C.; Holt, L. E., Jr.; Farrow, H. L., and Neale, S.: Studies in Fat Metabolism: II. Fat Absorption in Premature Infants and Twins, J. Pediat. **6**:481, 1935. (*c*) Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: I. Effect on Fecal Fat of Decreasing Fat Intake, Am. J. Dis. Child. **62**:328 (Aug.) 1941. (*d*) Muhl.[2c]

tion of fat was greatest (M. B., 31 per cent and H. L., 41 per cent) the percentage retentions of calcium were high (table 2). Furthermore, in 6 young full term infants who were fed the cow's milk–olive oil mixture and whose excretion of fat was low [17c] the fecal calcium averaged 103 mg. per kilogram, with a range of from 71 to 133 mg. per kilogram,[18] as compared with values of only 26, 56 and 71 mg. per kilogram for the 3 premature infants in this study.

Poor absorption of fat may also diminish retention of calcium because of the associated defect in absorption of vitamin D. The infants in the present study received supplements of 4,000 U. S. P. units of this vitamin per day. While this dose is less than that recommended by some authorities to insure prevention of rickets in premature infants,[19] it is unlikely that rickets was present in any of the infants studied. Roentgenograms were obtained for only 1 of the infants, but neither in these nor in the roentgenograms of 10 other premature infants fed similar diets was there any evidence of rickets.

B. Rate of Body Growth: Since rapid body growth is thought to exert a depressing effect on calcification,[20] possibly by diverting phosphorus to soft tissue, and since premature infants grow at a rate faster than that of full term infants, the effect of this factor, like that of poor absorption of fat, might be expected to reduce rather than to increase retention of calcium. Vitamin D, on the other hand, gives a simultaneous impetus to both retention of calcium and body growth,[21] so that the effect of growth per se might be easily masked. In the present study, growth occurred at the rapid rate characteristic of premature infants and vitamin D in relatively large doses was administered. It is therefore of interest to calculate the rate of calcium retention in terms of gain of body weight and to compare it with that reported for normal infants.

Such computations of the mineral composition of growth have been made by Swanson.[22] In the absence of antirachitic therapy it was

18. McNamara, H., and Gordon, H. H.: Unpublished data.

19. Davidson, L. T., and Merritt, K. K.: Viosterol in the Prophylaxis of Rickets in Premature Infants: Clinical, Chemical and Roentgenologic Observations, Am. J. Dis. Child. **48**:281 (Aug.) 1934.

20. (*a*) Outhouse, J., and Mendel, L. B.: The Rate of Growth: I. Its Influence on the Skeletal Development of the Albino Rat, J. Exper. Zoöl. **64**:257, 1933. (*b*) Fairbanks, B. W., and Mitchell, H. H.: The Relation Between Calcium Retention and the Store of Calcium in the Body with Particular Reference to the Determination of Calcium Requirements, J. Nutrition **11**:551, 1936.

21. Stearns, G.: The Mineral Metabolism of Normal Infants, Physiol. Rev. **19**:415, 1939.

22. Swanson, W. W.: The Composition of Growth: II. The Full Term Infant, Am. J. Dis. Child. **43**:10 (Jan.) 1932.

observed that calcium retention did not keep pace with body growth. This was also true, but to a lesser extent, of the premature infant studied by Hamilton.[2b] Swanson found, however, that when cod liver oil was administered storage of calcium was sharply increased. If the values obtained by Swanson during the age period from 10 days to 3 months are corrected for lack of vitamin D to permit comparison with those of the young premature infants of the present study,[23] a value is obtained of 0.5 Gm. for the calcium content of a kilogram of weight gained by a normal young full term infant receiving human milk plus vitamin D. In chart 1 it is seen that infant M. B. on a similar diet had a higher rate of calcium deposition per kilogram of weight gained even though he was growing proportionately more rapidly (15 Gm. per kilogram per day [table 1]) than a full term infant. When cow's milk was fed, the increased rate of deposition of calcium in premature infants was sufficient to keep pace with the increase in their rate of growth, since the concentrations of calcium per kilogram of body weight gained were in this instance closely similar for premature and for full term infants. The average for the premature infants was 9.4 Gm. per kilogram of weight gained, as compared with 8.9 Gm. per kilogram for full term infants.

C. Activity of the Parathyroid Glands: If the high calcium retentions of premature infants were due to a developmental underactivity of the parathyroid glands, an abnormally low ratio of urinary to fecal excretion of both calcium and phosphorus should be present.[24] These ratios were accordingly calculated and appear in table 2. The ratios for calcium were 0.06, 0.14 and 0.16 for premature infants fed cow's milk, as compared with a range of 0.005 to 0.16 for full term infants.[12b] The phosphorus ratios were 0.8, 2.6 and 2.9 for the premature infants, as compared with a range of 1.6 to 5.5 for full term infants.[12b] The ratios thus afford no evidence of hypoactivity of the parathyroid glands.

23. The average value for the retentions observed during the first three periods of administration of cod liver oil (representing the age period of 3 to 4 months) was divided by the average value for the retentions observed during the last three periods before cod liver oil was given (representing the age period of 2 to 3 months). The quotient (2.5) was multiplied by the figures for the retentions per kilogram of gain of body weight during the age period from 10 days to 3 months, and it was assumed that this correction when applied to these early retentions would indicate the approximate retention which would have occurred had an antirachitic supplement been given during this time. There is no evidence to support the validity of this assumption.

24. Aub, J. C.; Albright, F.; Bauer, W., and Rossmeisl, E.: Studies of Calcium and Phosphorus Metabolism: VI. In Hypoparathyroidism and Chronic Steatorrhea with Tetany, with Special Consideration of the Therapeutic Effect of Thyroid, J. Clin. Investigation **11**:211, 1932.

D. Previous Degree of Saturation of the Bones: That the retention of calcium at any given level of intake is inversely proportional to the previous level of dietary calcium and the resulting degree of saturation of the bones has been pointed out most recently by Fairbanks and Mitchell [20b] and by Rottensten.[25] At the beginning of this study two circumstances contributed toward a high degree of undersaturation of the bones of the premature infants with respect to calcium. In the first place, since there is a pronounced increase in the deposition of calcium during the last two months of fetal life,[1] premature birth probably deprived them of important amounts of this element. In the second

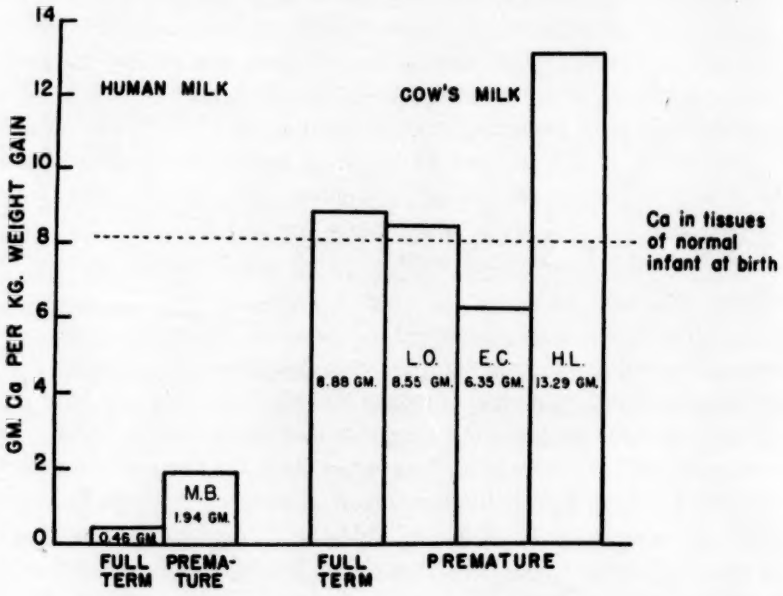

Chart 1.—Relation of diet to retention of calcium per kilogram of gain of body weight. Data for full term infants were calculated from Swanson's observations.[22]

place, the infants were given human milk from the time of birth until the beginning of the studies. Hamilton [2a] has pointed out that the total volume of human milk which can be consumed by a young infant contains an amount of calcium so small that even if it were completely utilized it would nevertheless be insufficient to permit the calcium to be deposited in the bones at a rate equal to that of general body and skeletal growth. Leitch [26] has summarized the data in support of this

25. Rottensten, K. V.: The Effect of Body Stores on the Efficiency of Calcium Utilization, Biochem. J. **32**:1285, 1938.

26. Leitch, I.: The Determination of the Calcium Requirements of Man, Nutrition Abstr. & Rev. **6**:553, 1937.

view and has pointed out the contributing effect of the diminution in water content of the bone which occurs in the course of normal growth. Stearns [21] has shown graphically the pronounced decrease in relative calcium content of the body which develops in a premature infant on a diet of human milk. It is clear, therefore, that at the beginning of the experimental period the infants, having been previously maintained on a diet which further exaggerated their birth deficiency, must have had seriously inadequate stores of calcium. This condition could well have given the impetus for the high retention of calcium observed in these infants.

3. How Well Do Human or Cow's Milk Feedings Satisfy the Requirements of the Premature Infant?

The weight of evidence of the present study together with that of previous investigations on this subject leaves little doubt that, given an adequate supply of calcium and phosphorus, the premature infant will utilize it well. The determination of requirement would seem to depend, therefore, on the estimation of what constitutes an adequate supply. The calculations which follow are necessarily only approximations, since they are based on averages and the variability among individuals is high. The calculations do, however, give a definite idea of the extent to which the combination of inadequate initial stores of calcium and rapid postnatal growth raises the requirement of premature infants for calcium and phosphorus, and they permit generalizations concerning the adequacy of human and of cow's milk in meeting these peculiarities of requirement.

Calcium Requirement: If the view is accepted that the calcium requirement for the premature infant is that level of intake which will permit him to correct his initial skeletal deficit by the time he has caught up in other respects with the normal infant, it should be possible on theoretic grounds to calculate how much calcium he would have to deposit and from this to estimate the adequacy of the two types of feeding. In order to make such a computation two points must be fixed. One is the time at which the premature infant may be considered to have become normal. For this no absolute criterion can be chosen, but it is probably at least a year before the premature infant approaches the normal in many physical respects.

The second point of reference is the calcium requirement of the normal infant. Unfortunately, for the age period under 4 months this requirement is a controversial matter. Rominger [27] and his school have accepted

27. Rominger, E.; Meyer, H., and Bomskov, C.: Rachitisstudien: I. Langfristige Kalk- und Phosphorstoffwechseluntersuchungen bei gesunden und rachitischen Säuglingen zugleich ein Beitrag zur Wirkungsweise des Vigantols, Ztschr. f. d. ges. exper. Med. **73**:343, 1930.

the view that retentions of minerals greater than those which occur with human milk feeding must be regarded as "supermineralization." Most American observers consider that the degree of calcification which occurs when cow's milk is fed is not unduly high and may be beneficial.

Leitch [26] has gone further, expressing the opinion that the retention of calcium by infants receiving human milk should not be taken as the optimum; rather, that an optimum intake is one which would permit maintenance of the degree of calcification of the bones at full term birth. This author has emphasized that during the first four months of life low total consumption of milk tends to prevent storage of calcium from

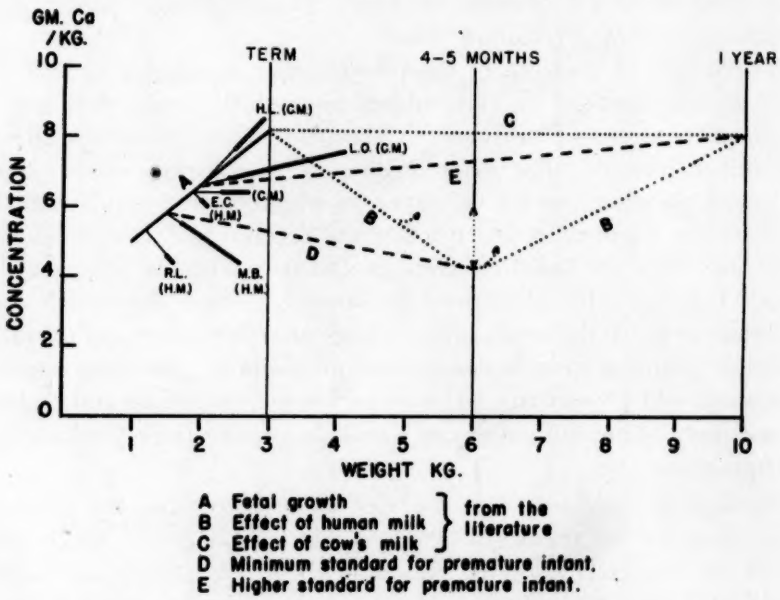

Chart 2.—Effect of growth and diet on calcium stores of premature infants.

keeping pace with the rapid growth of the body and that the initial level of calcium concentration is thus seldom maintained by normal infants. This is particularly true of those fed solely on human milk. Later, increased consumption of milk and decreased rate of growth combine to permit restoration of the original calcium reserves by about 1 year of age.

Chart 2, which is adapted from a diagram in Stearns's review,[21] graphically demonstrates these points. It represents the limits of normal for the changes in calcium concentration in the infant's body which take place between late fetal life and 1 year of age. The heavy line *A* was obtained by Stearns from the data in the literature on analyses of fetuses and shows the increase in concentration of calcium in the body of the

fetus as it increases in weight from 1 to 3 Kg. After birth the concentration of calcium is dependent on diet. Curve *C* represents the calcium storage with a high calcium intake of full term infants who have succeeded in maintaining their birth concentration of 8 Gm. per kilogram. In Stearns's diagram the line representing the average performance of full term breast-fed infants falls to a minimum of approximately 6 Gm. per kilogram at 4 months of age.[28] In chart 2 the corresponding line, *B*, has been drawn to the much lower level of 4 Gm. per kilogram in order to include the lowest retention value which we could find in the literature [27] for a young, rapidly growing full term infant who was reported as nonrachitic. This baby was breast fed and was receiving no vitamin D. In order to emphasize the fact that 4 Gm. per kilogram is an exceedingly low calcium concentration for a normal infant of 4 months, it should be pointed out that since the infant has at this point approximately doubled his birth weight while at the same time he has halved his calcium concentration he must have retained no calcium since birth.

Roughly, then, the area included between lines *B* and *C* may be considered to represent the range of normal for the calcium concentration of a full term infant and 4 Gm. per kilogram to be at or near the critical level below which it is unlikely that the bones are in an optimal state of mineralization.

Against this background three hypothetic rates of storage of calcium may be plotted to serve as a basis in establishing the dietary requirements of the premature infant. The first, along line *A*, is perhaps the most natural rate, corresponding to the one which he would have followed had he remained in utero to term. If he follows the second, lower, rate, represented by the line *E*, the diet would have to supply sufficient calcium so that from birth to 1 year of age he would systematically correct his initial deficit. If he follows the lowest rate, *D*, the diet would be called on to supply only sufficient calcium to prevent depletion of the stores below the level of 4 Gm. per kilogram.

In order to compare the performance of the infants in the present study with these theoretic requirements, the calcium concentration in the body of each was calculated in the following manner: For each infant the concentration at the time of birth was obtained from the birth weight, located on line *A*. For instance, for infant M. B., birth weight 1,500 Gm., the assumed calcium concentration was 5.8 Gm. per kilogram. During the period of study he laid down 1.94 Gm. of calcium per kilogram of weight gained, and at the end of the period of study his

28. If, as is often the case, the calcium intake is raised by a change from human to cow's milk, an upswing in curve *B* will occur, as indicated by the curved arrows.

weight was 2,586 Gm. The final concentration of calcium in his body at this time would have thus become $\frac{(1.5 \times 5.8) + [1.94 \times (2.586 - 1.5)]}{2.586} = 4.2$ Gm. of calcium per kilogram. The line connecting this point with the birth weight on line *A* describes the change in calcium content of the tissues of this infant from birth to 47 days of age, the interval during which he was studied being underscored. It will be seen that human milk failed to meet any of the requirements *D, E* or *A*. In spite of the efficient utilization already described, all 3 infants who received this diet were depleting their stores of calcium at a rate faster that that permitted by the lowest standard here considered adequate. At body weights of 2.9, 2.7 and 1.7 Kg., respectively, they would at this rate have acquired a degree of osteoporosis greater than that represented by a calcium concentration of 4 Gm. per kilogram. Although there would seem to be no definite proof that this is harmful, it is difficult to conceive of it as an optimum state for which to strive in determining mineral requirements. With the cow's milk diet, on the other hand, the high calcium retentions of all 3 infants exceeded that needed to meet the lowest requirement. Two of the 3 infants had retentions which surpassed the requirements defined by the second line *E*.

Phosphorus Requirement: In table 2 the "theoretic" phosphorus retentions are presented. They were calculated according to the formula of Albright, Bauer, Ropes and Aub,[29] P ret. $= \frac{\text{Ca ret.}}{2} + \frac{\text{N ret.}}{17.4}$ and in all but 1 case (H. L.) they agree within 10 to 15 per cent with the observed retentions of phosphorus. It may therefore be concluded that phosphorus was retained by the premature infants in the usual relation to calcium and to nitrogen and that the deductions regarding the storage of calcium which were made in the preceding section would apply equally well to the storage of phosphorus.

From the standpoint of skeletal formation it may be concluded from these calculations that for premature infants human milk is not the food of choice unless it is supplemented with both calcium and phosphorus, as, for instance, by the addition of calcium paracaseinate.

SUMMARY AND CONCLUSIONS

A study was made of the retentions of calcium and phosphorus by 3 premature infants receiving a diet of human milk and by 3 fed a cow's milk preparation. The infants retained a greater portion of the intake of both minerals than is reported for full term infants. The degree of utilization of the calcium of cow's milk was greater than that

29. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: IV. The Effect of Parathyroid Hormone, J. Clin. Investigation **7**:139, 1929.

of human milk, possibly because the lack of phosphorus in the latter acted as a limiting factor in retention of calcium.

The calcium requirement for premature infants was calculated on theoretic grounds, and three standards were set. The first, selected as the minimal acceptable level, was the lowest degree of calcification reported for a young, supposedly nonrachitic full term infant receiving human milk. The second, and probably more desirable, standard was that which would permit the premature infant to commence from birth systematically to correct his initial deficit and attain by the end of a year the degree of calcification shown by a full term infant. The third was the highest rate, namely, that at which calcium would have been laid down had the infant remained in utero to term.

Mineral retention with a diet of human milk supplemented with vitamin D was inadequate to meet even the lowest calculated requirement. Retentions by the premature infants with the cow's milk diet, on the other hand, were sufficient to insure normal calcification of his bony structure at 1 year of age. Since retention of phosphorus by the premature infants showed the expected relationship to retention of calcium and nitrogen, the conclusions concerning the calcium requirement are equally applicable to the phosphorus requirement.

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Case Reports

WATERHOUSE–FRIDERICHSEN SYNDROME ON ISTHMUS OF PANAMA

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AND
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The Waterhouse-Friderichsen syndrome is a relatively rare, dramatically abrupt, fulminating condition in which there is massive, usually bilateral, adrenal hemorrhage associated with a striking, variegated cyanosis and acute cardiorespiratory collapse. The cause is generally considered to be meningococcic septicemia. Excellent discussions of the clinical picture have been presented by Aegerter,[1] Sacks,[2] Kunstadter [3] and Lindsay, Rice, Selinger and Robins.[4]

Waterhouse [5] in 1911 collected 15 cases from the literature, and Friderichsen [6] in 1918 brought the total to 30 cases. The most recent review is that of Lindsay and his co-workers,[4] who found 89 cases in the literature and added 7 of their own. Since that time 9 additional cases [7] have been reported, bringing the total number of cases in the

From the Board of Health Laboratory, Gorgas Hospital.

1. Aegerter, E. E.: Waterhouse-Friderichsen Syndrome: Review of Literature and Report of Two Cases, J. A. M. A. **106**:1715-1719 (May 16) 1936.

2. Sacks, M. S.: Fulminating Septicemia Associated with Purpura and Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome): Report of Two Cases with Review of Literature, Ann. Int. Med. **10**:1105-1114 (Feb.) 1937.

3. Kunstadter, R. H.: Waterhouse-Friderichsen Syndrome, Arch. Pediat. **56**:489-507 (Aug.) 1939.

4. Lindsay, J. W.; Rice, E. C.; Selinger, M. A., and Robins, L.: Waterhouse-Friderichsen Syndrome: Acute Bilateral Suprarenal Hemorrhage, Am. J. M. Sc. **201**:263-270 (Feb.) 1941.

5. Waterhouse, R.: A Case of Suprarenal Apoplexy, Lancet **1**:577, 1911.

6. Friderichsen, C.: Nebennierenapoplexie bei kleinen Kindern, Jahrb. f. Kinderh. **87**:109, 1918; cited by Aegerter.[1]

7. (*a*) Grace, W. H.; Harrison, C. V., and Davie, T. B.: Suprarenal Haemorrhage in Meningococcal Septicaemia: Waterhouse-Friderichsen Syndrome, Lancet **2**:102-103 (July 27) 1940. (*b*) Hughes, J. F.: Fulminating Septicaemia Associated with Purpura and Adrenal Haemorrhage (Waterhouse-Friderichsen Syndrome), Brit. M. J. **2**:353-354 (Sept. 14) 1940. (*c*) Moss, E. S., and Schenken, J. R.: Fulminating Meningococcal Septicemia with Bilateral Suprarenal Hemorrhages: Report of Two Cases, New Orleans M. & S. J. **93**:294-300 (Dec.) 1940. (*d*)

(Footnote continued on next page)

literature to 105. Practically all of these reports have come from Europe and the United States. Barsoum [8] found this condition in an Egyptian farmer, and Leone [7d] recently discovered it in a white soldier in the Philippine Islands.

Since we have been unable to find any previously published reports from Central America, we are presenting 2 cases in which this syndrome occurred in Panamanian mestizo infants at Gorgas Hospital, Ancon, Canal Zone.

REPORT OF CASES

CASE 1.—*Clinical Summary.*—E. R. was a 25 day old Panamanian mestizo girl who had been delivered normally at home. The mother was a septipara, and the family background was noncontributory. Her birth weight was 11 pounds (4,990 Gm.); she was breast fed and progressed normally to her twenty-first day. At that time, four days before her admission to the hospital, a white coating appeared on the entire buccal mucous membrane. Associated with this, shallow ulcers developed; the child refused her feedings and became increasingly fretful. The night before admission she was said to have been hot and feverish. In the morning diarrhea, with profuse, watery stools had developed, and the mother noticed small red spots on the child's forehead. No other symptoms were observed.

On admission, at 10:30 a. m. Oct. 16, 1941, the child appeared pale, dehydrated and undernourished. In spite of a temperature of 103 F., she did not appear acutely ill and was active and fretful. On the middle part of her forehead were several discrete bright red papular spots about 0.3 cm. in diameter. Hyperemia and shallow ulceration of the buccal mucous membrane with flecks of white exudate were present. The abdomen was tense and the umbilicus well healed. The ears, lungs and heart were normal. Examination of the blood on the patient's admission to the hospital revealed: erythrocytes, 3,790,000 per cubic millimeter; leukocytes, 7,000 per cubic millimeter, with 67 per cent neutrophils and 33 per cent lymphocytes. Smears of the blood did not contain plasmodia. No ova or parasites were found in the stool.

Gentian violet was applied to the oral lesions, and at 1 p. m. 2.5 grains (0.16 Gm.) of sulfathiazole was given orally and retained. At 2 p. m. the child appeared more apathetic and purplish red mottling of the skin had developed. During examination she again became active, and the skin regained its former pallor with blotchy cyanosis. At 4 p. m. the skin of the entire body was discolored by purplish red cyanosis, having the appearance of postmortem lividity, and pressure marks from the bell of the stethoscope persisted for long periods as white rings. Acute circulatory collapse supervened, with undetectable peripheral pulse and fast, feeble heart sounds. Respirations were shallow and irregular, with periods of apnea. In spite of the administration of oxygen and stimulants, the child declined rapidly and died at 5:10 p. m., within seven hours after her admission to the hospital.

Leone, G. E.: Spontaneous Hemorrhage into Suprarenals (Suprarenal Apoplexy), Ann. Int. Med. **14**:2137-2142 (May) 1941. (*e*) Meningococcus Septicemia: Hemorrhage into Adrenal Glands, Cabot Case 26362, New England J. Med. **223**:383-385 (Sept. 5) 1940. (*f*) Kwedar, A. T.: The Waterhouse-Friderichsen Syndrome: Report of a Case in an Adult, Ann. Int. Med. **16**:787-791 (April) 1942.

8. Barsoum, H.: Adrenal Apoplexy, Brit. M. J. **2**:972 (Nov. 14) 1936.

Autopsy.—A complete autopsy was done at 8:30 a. m. October 17, fifteen hours after death. The description will be limited to the essential pertinent observations. The child weighed 8½ pounds (3,856 Gm.) and measured 22½ inches (57 cm.) in length. A few subconjunctival hemorrhages were noted bilaterally. The skin was mottled red and purple, but petechiae were not seen, either grossly or microscopically. Evidence of meningitis or pneumonia was not noted. The spleen was not enlarged. The left kidney measured 8.5 by 6 by 3.0 cm. and both grossly and microscopically possessed the characteristics of a congenital polycystic kidney; no normal renal tissue was recognized. The right kidney was not remarkable. The thymus was relatively large, weighing 15 Gm.; its histologic structure was normal.

Adrenals: Through the peritoneum the adrenals appeared tense, firm and purplish black. The two glands were essentially similar. Each measured 3 by 2.5 by 1 cm.; together they weighed 10 Gm. Sectioning exposed homogeneous dark reddish black tissue, which appeared hemorrhagic. Inspection of the cut surfaces revealed two zones: a central portion, which was black, and a peripheral portion, apparently cortical tissue, which was dark red. Hemorrhage into the periadrenal fat was not present. Fractures of the ribs were not noted, nor were any diffuse retroperitoneal hemorrhages found.

Microscopic Observations: Extensive diffuse hemorrhages were present in the adrenal glands bilaterally. The capillaries of the cortices were extremely congested. Many of the capillaries had ruptured and spilled small amounts of blood into the adjoining tissue. In addition, within the central portion of the adrenals there was extensive hemorrhage with total disorganization of the architecture, destruction of the tissue and widening of the organ. The blood had excited no leukocytic reaction. Medullary tissue could not be recognized with certainty. It was difficult to state exactly how much of the cortex was destroyed. A striking feature was the total absence of lesions in the periadrenal tissue; even the capillaries of the periadrenal tissue were but slightly congested.

Bacteriologic Observations: Culture of the blood revealed Staphylococcus albus, considered a contaminant.

Anatomic Diagnoses: The anatomic diagnoses were: Waterhouse-Friderichsen syndrome (extensive bilateral adrenal hemorrhages); congenital polycystic kidney (left); moderate congestion of the lungs; moderate congestion of the leptomeninges; severe congestion of the mucosa of the larynx and trachea; bilateral small subconjunctival hemorrhages; small cysts of the base of the tongue; cyanotic mottling of the skin.

Case 2.—*Clinical Summary.*—R. A. was a 2 month old Panamanian mestizo girl who was admitted to Gorgas Hospital on Jan. 21, 1940 and died on January 23. The records on this case are scanty.

The child had had one previous period of hospitalization, having been admitted January 3 and discharged January 10. She was not ill on admission, entering the hospital only for nursing care, since her mother was ill in another ward. Her weight on admission was only 10 pounds 8 ounces (4,763 Gm.) and she appeared to have been neglected. She gained weight to 10 pounds 13 ounces (4,904 Gm.), but on the day of discharge her weight was only 10 pounds 5 ounces (4,678 Gm.). There was no fever or diarrhea during this admission. Hematologic studies revealed a hemoglobin content of 65 per cent, 3,820,000 red cells per cubic millimeter of blood and 9,000 white cells, with 40 per cent neutrophils and 60 per cent lymphocytes.

Two days before the last admission the child became ill with fever, vomiting and diarrhea. These symptoms persisted until admission. On entering the hospital, the patient appeared acutely ill. Her temperature was 102.4 F., and during the next forty-eight hours it varied from 100 to 102 F. She appeared extremely weak and apathetic and vomited frequently. No localizing signs were found. A spinal tap yielded normal fluid. A roentgenogram of the chest was suggestive of early bronchopneumonia in the upper lobe of each lung. The hemoglobin content was 65 per cent; there were 3,810,000 red cells and 11,100 white cells per cubic millimeter of blood, with 79 per cent neutrophils and 21 per cent lymphocytes. Despite the administration of fluids, epinephrine and sulfapyridine, she became weaker and died at 6:10 a. m. January 23.

Autopsy.—A complete autopsy was performed[9] at 10 a. m. January 23, four hours after death. Mention will be made only of the significant observations. The body was that of a brown, poorly nourished girl, measuring 21½ inches (54 cm.) in length and weighing 9 pounds (4,082 Gm.). A fine scaly eruption was noted on the skin over the trunk and extremities. Yellow, purulent exudate was present in the middle ears bilaterally. The tympanic membranes were not ruptured.

Adrenals: The left adrenal was large and dark purple. Sectioning revealed extensive hemorrhage, which replaced the medulla and extended almost to the capsule. The blood was purplish. No hemorrhage into the pericortical tissue was present. The right adrenal was small with a light yellow cortex. The medulla had undergone partial autolysis.

Microscopic Observations: Large hemorrhages, which extended through the cortex practically to the capsule, were present in the medulla of the left adrenal. The blood cells showed considerable laking. No inflammatory reaction was noted. The right adrenal appeared normal.

Bacteriologic Observations: The blood on culture yielded Staph. albus, considered a contaminant. The pus in the middle ears contained gram-positive cocci, occurring singly, in pairs or in short chains and resembling pneumococci or streptococci; cultures were overgrown with organisms of genus Proteus. In histologic sections of the leptomeninges a few focal collections of small round cells and a few small hemorrhages into the pia-arachnoid were observed. In one area of the pia a small clump of bacteria, apparently cocci in pairs or clumps, was noted, but no true meningitis was found. Smears of the spleen contained gram-positive diplococci, but no lesions were seen in routine examination of sections stained with hematoxylin and eosin. These observations suggested the presence of a septicemia.

Anatomic Diagnoses: The anatomic diagnoses were: hemorrhage of the left adrenal; bilateral suppurative otitis media; severe tubular degeneration of the kidneys; malnutrition; hypoplasia of the thymus.

COMMENT

The Waterhouse-Friderichsen syndrome has been found to occur most often in the presence of a septicemia, generally meningococcic. Of a total of 524 cases of suppurative bacterial meningitis which were observed at the Gorgas Hospital during the years 1904 to 1941, Kean and

9. The autopsy was performed by Dr. Hugh R. Gilmore Jr., pathologist.

Crandall [10] found that in 119, or 22.7 per cent, the condition was caused by the meningococcus. Seventy-four, or 62.2 per cent, of the 119 patients were nontransient; this indicates that meningococcic meningitis does occur in the native population. It is possible, therefore, that despite the absence of bacteriologic proof, our 2 patients actually had meningococcic septicemia.

Kunstadter [8] reported the occurrence of this syndrome in a 12 day old child. This is the only patient we have been able to find younger than our first infant, who was 25 days old.

SUMMARY

Two cases in which the Waterhouse-Friderichsen syndrome occurred in Panamanian mestizo infants are reported. These are the first cases to be reported from Central America and bring the total of published cases to 107.

Since our survey of the literature several articles on the Waterhouse-Friderichsen syndrome have been recorded in the *Quarterly Cumulative Index Medicus*.[11]

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10. Kean, B. H., and Crandall, W. D.: Bacterial Meningitis on the Isthmus of Panama, to be published.

11. Drummond, W. F., and Tooke, T. B., Jr.: Waterhouse-Friderichsen Syndrome (Acute Bilateral Suprarenal Hemorrhage): Review of Literature and Report of Two Cases, New Orleans M. & S. J. **94**:11-17 (July) 1941. Monfort, J. A., and Mehrling, J. H.: Waterhouse-Friderichsen Syndrome: Review of Literature and Report of Case with Autopsy, Am. J. Dis. Child. **62**:144-149 (July) 1941. Holley, W. J.: Massive Hemorrhage: Clinico-Pathologic Case Report, Bull. Vancouver M. A. **18**:276-277 (June) 1942. Banks, H. S., and McCartney, J. E.: Meningococcal Encephalitis, Lancet **1**:219-223 (Feb. 21) 1942. Landis, J.: Waterhouse-Friderichsen Syndrome, Schweiz. med. Wchnschr. **72**:179-182 (Feb. 14) 1942. Michael, P., and Jacobus, L.: Waterhouse-Friderichsen Syndrome, Arch. Pediat. **59**:141-147 (March) 1942.

GUILLAIN-BARRÉ SYNDROME ("INFECTIOUS POLYNEURITIS") AND ACUTE ANTERIOR POLIOMYELITIS

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AND
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Since Guillain, Barré and Strohl [1] described a peculiar form of polyneuritis coexisting with normal cell count and increased protein of the cerebrospinal fluid, considerable attention has been devoted, particularly in the pediatric literature, to the problem of differentiation between this type of polyneuritis and acute anterior poliomyelitis.

There appears to be a consensus that the two diseases are entirely distinct. However, from the etiologic point of view this contention lacks convincing evidence; in fact, the causative agent of the Guillain-Barré syndrome is still unknown; and, curiously, no attempts have been made to ascertain whether poliomyelitic virus can be isolated from patients affected with this type of polyneuritis. From a pathologic point of view, a distinction between the two conditions seems justified. In infectious polyneuritis the primary site of damage is in the peripheral nerves and spinal ganglions, in contradistinction to the involvement of the anterior horn in poliomyelitis. Pathologic reports on the Guillain-Barré syndrome, however, are extremely scanty and often incomplete. It is mainly by the clinical manifestations, the laboratory observations and the final outcome that a differentiation between the Guillain-Barré syndrome and poliomyelitis is usually made.

The purpose of this paper is to describe the case of a patient who showed the clinical manifestations and laboratory findings that are considered typical of the Guillain-Barré syndrome and whose disease post mortem appeared to be acute anterior poliomyelitis. On the basis of these observations and the pertinent data of the literature, a brief discussion of the problem of the relation between the two diseases is presented.

From the New York State Reconstruction Home, West Haverstraw, N. Y., and the Research Department, Letchworth Village, Thiells, N. Y.

1. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462, 1916.

REPORT OF A CASE

R. H., a white boy 12 years of age, was admitted to Meadowbrook Hospital, Hempstead, N. Y., on Aug. 11, 1941, because of fever, drowsiness and general malaise of three days' duration and inability to walk of six hours' duration. The past history was not contributory. On admission, the patient appeared acutely ill; the temperature was 102 F., the pulse rate 125 and the respiratory rate 24. Systemic examination revealed nothing of significance apart from the neurologic conditions.

The upper extremities showed severe motor impairment; the patient was unable to raise his arms or move his shoulders but was able to bend his elbows and move his wrists. The fingers could be flexed but not extended. The muscular tonicity was diminished, but the triceps, biceps and radial reflexes were still present. Both lower extremities also showed flaccid paralysis, which was

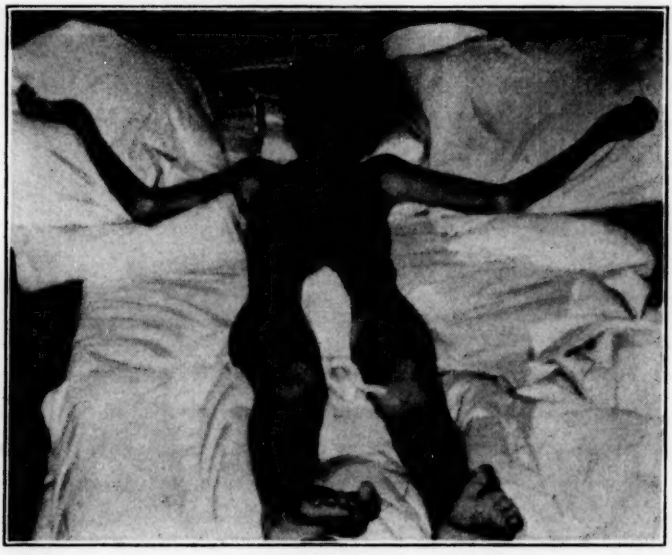

Fig. 1.—Aspect of the patient one month before death.

complete in the proximal segments and incomplete in the distal segments: The patient was unable to move his hips but moved his toes well. Knee and ankle jerks were bilaterally absent. The plantar reflexes were in flexion. Pain was experienced during compression of the point of exit of the sciatic nerve and on compression over the lumbar portion of the spine. Breathing was so laborious that the use of an Emerson respirator became necessary.

The following days the paralysis appeared to progress. The temperature ranged from 99 to 102 F. for four days and then subsided. On August 18 five attacks of generalized convulsions of the grand mal type were observed. On September 5 ophthalmoscopic examination showed bilateral optic neuritis with papilledema. At that time the spinal fluid pressure was found to be 35 mm. of mercury.

On October 3 the patient was transferred to the New York State Reconstruction Home, West Haverstraw, N. Y., where he was under our care. He appeared as a thin, emaciated boy, weighing 70 pounds (31.8 Kg.) (fig. 1).

On neurologic examination, there was considerable and extensive motor impairment: The muscles innervated by the cranial nerves were normal; breathing was somewhat difficult, and the inspiratory effort involved the accessory muscles; the muscles of the neck, back and abdomen showed only traces of contraction; in the upper extremities, the muscles of the shoulders were almost completely paralyzed and showed pronounced atrophy and those of the elbow were also involved but to a lesser extent while the muscles of the wrist were better preserved; the movements of the fingers were fair to good. In the two lower extremities, the muscles of the hip and knee showed no power while those of the ankle and foot showed a fair amount of voluntary contraction, more on the left side. All tendon reflexes of the upper and lower extremities were absent with the exception of the left radial, which was diminished. The abdominal reflexes were absent. There were no signs of involvement of the pyramidal tract. Some contractures were present. Pains were experienced on passive motion of the paralyzed muscles, but no alterations of the various sensibilities could be elicited. The patient, however, showed poor cooperation during the examination. There was slight anisocoria, but the pupils reacted promptly to light and in accommodation. The fundi were normal.

The original diagnosis of poliomyelitis was questioned, and a tentative diagnosis of Guillain-Barré syndrome was made. The full Kenny regimen was instituted; in addition, large doses of vitamin B complex were given.

During the following two months a slowly progressing improvement of the paralysis was noted. The contractures responded well to treatment; dyspnea disappeared, and by the middle of December the patient had recovered enough muscle power in his upper extremities to enable him to feed himself and hold a newspaper. On Feb. 20, 1942, an infection of the upper respiratory tract developed, and pneumonia followed shortly thereafter. The patient died on February 24, of bilateral lobar pneumonia.

LABORATORY EXAMINATION

Several blood counts were performed during the various stages of the disease but showed nothing of significance. The Wassermann reaction of the blood was negative. Urinalysis showed nothing abnormal.

Repeated examinations of the spinal fluid were performed, and a pronounced albuminocytologic dissociation was constantly found, as shown by the following table:

Date	Cells	Reactions for Globulin		Total Protein, Mg. per 100 Cc.	Sugar	Appearance
		Pandy	Nonne			
8/11/1941	1					Clear
8/19/1941	7			150	"normal"	Clear
8/29/1941	2			Over 200		Clear
9 /5/1941	2			1,200	"normal"	Clear
10/11/1941	4	4 +	4 +	Over 100		Clear
1/ 7/1942	1	4 +	4 +	125		Clear

PATHOLOGIC EXAMINATION

Necropsy was performed fourteen hours after death. The body was that of a thin, emaciated child weighing about 50 pounds (23.1 Kg.). Extreme muscular wasting was present, involving the muscles of the extremities and those of the trunk. Gross examination showed nothing of significance apart from acute lobar pneumonia.

Histologically, the main changes were found in the spinal cord. The anterior horns were the site of a pathologic process consisting of both vascular and parenchymatous changes. With hematoxylin and eosin, Mallory and Nissl stains the blood vessels appeared congested and numerous cells infiltrated the perivascular spaces of the small veins and, to a lesser extent, of the arterioles (fig. 2). The perivascular cuffing was made up of lymphocytes, fat-scavenging elements, a few plasma cells and occasional adventitial cells. Leukocytes were absent. No thromboses were detected, but with the Pickworth stain small hemorrhages were seen occasionally. These vascular changes involved mainly the gray matter of the anterior horn. At times small vessels of the anterior columns showed also infiltrations, but in these instances the cuffing consisted predominantly of fat-

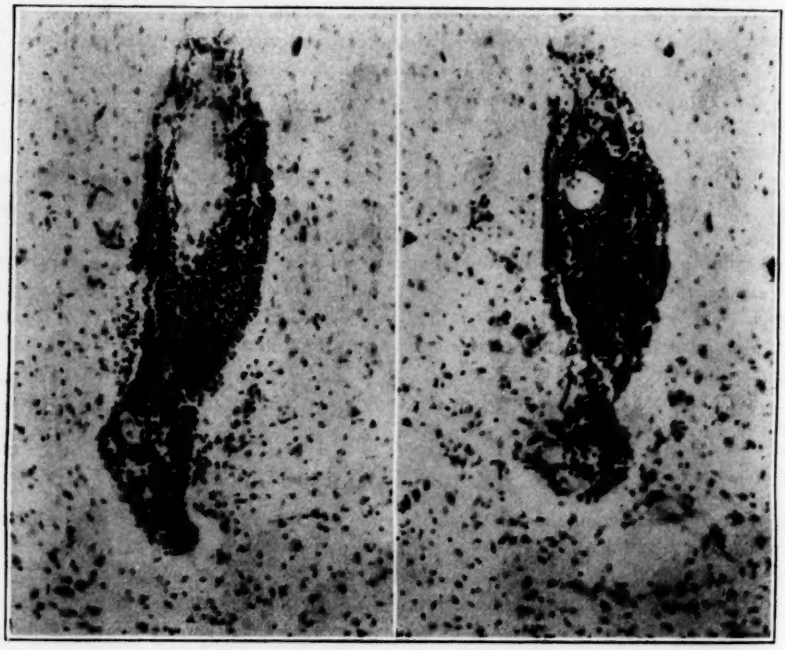

Fig. 2.—Perivascular infiltrations in the anterior horn of the spinal cord (Nissl stain; × 120).

scavenging elements. No vascular changes were seen in the posterior horn or in the spinal ganglions. The meninges were not infiltrated. The parenchymatous changes consisted of degeneration of neuron cells and breaking down of myelin sheaths with glia reaction. In the Nissl preparation, all stages of neurocellular degeneration could be observed, from chromatolysis to complete destruction (fig. 3). The cells involved were those of the ventral horn; the cells of the lateral horn were occasionally affected, and those of the dorsal horns rarely showed slight degenerative changes. The breakdown of myelin sheaths was perhaps more severe than generally seen in poliomyelitis: In both Marchi (osmic acid) and in Herxheimer (scarlet red) preparations numerous droplets of fat were present in the anterior horn and in the white matter surrounding it. This fat was partly free in the tissue and partly scavenged in cellular elements of the microglia type. Corresponding sections stained with methods for myelin sheaths showed absence of myelin

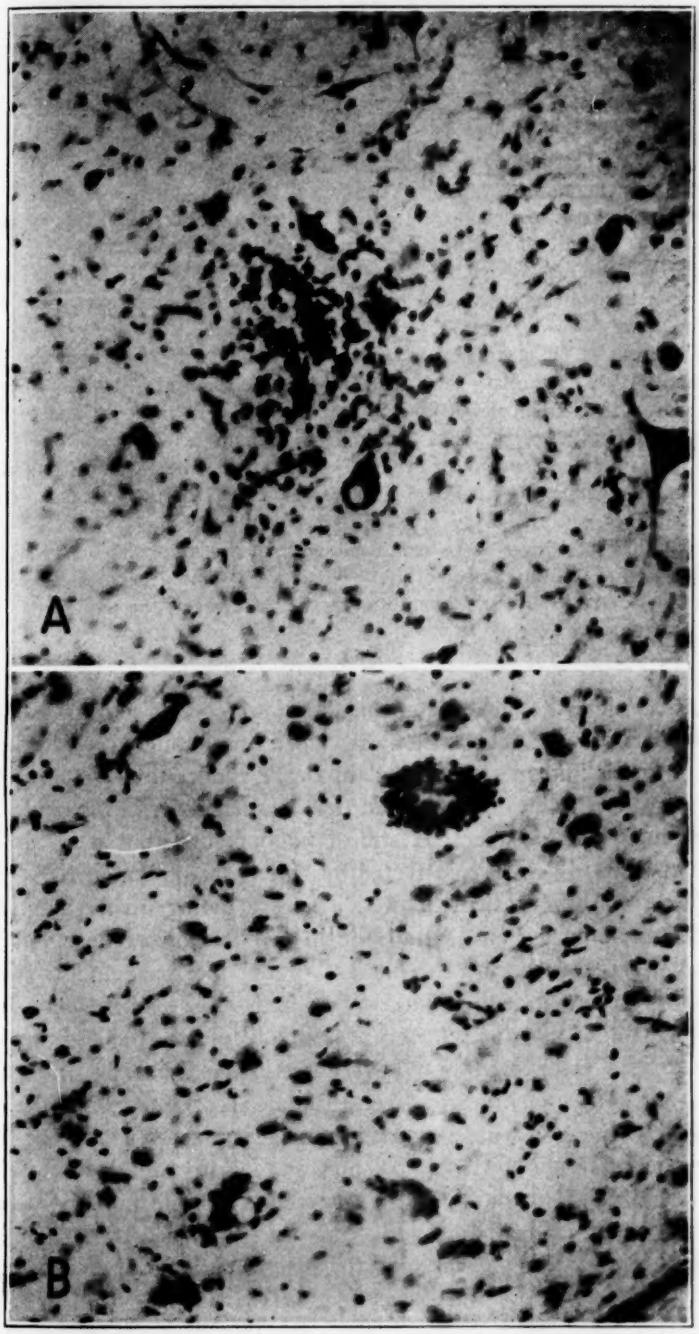

Fig. 3.—Anterior horn of the spinal cord. *A*, lesions of nerve cells and glia nodules; *B*, disappearance of nerve cells, proliferation of macroglia and perivascular infiltration (Nissl stain; × 200).

in the regions that stained black with osmic acid. The glia reaction was conspicuous (fig. 3). The macroglia showed both hypertrophic and hyperplastic changes: Numerous large elements with abundant cytoplasm and swollen nuclei were seen in the areas of neurocellular destruction. The microglia was also active, as evidenced by the presence of numerous fat-scavenging cells and microglia nodules. There were often characteristic "glia rosettes," consisting mainly of microglia elements; these were found also outside the anterior horns, namely, in the posterior columns and, rarely, in the dorsal horns.

These pathologic changes were found in every segment of the spinal cord examined but varied considerably in severity from one section to another. There was no correlation observed between the various features. In fact, conspicuous perivascular infiltrations were seen in areas where the nerve cells were only slightly altered.

In the medulla oblongata a few perivascular cuffings were seen in the inferior olives and in the substantia gelatinosa, where proliferation of glia was also present. The nuclei of the cranial nerves appeared uninvolved. In the pons and cerebellum no pathologic changes were found. In the hypothalamus a few blood vessels showed a slight infiltration, consisting of scanty lymphocytes. The thalamus and striatum were normal. Numerous cortical fields were examined, but no evidence of inflammatory changes was found.

The peripheral nerves were examined with methods for fat (Marchi, Herxheimer) and for myelin (Spielmeyer). There were some degenerative changes as expected in severe lesions of the anterior horns. However, the pathologic features of polyneuritis were absent.

COMMENT

Both clinical manifestations and laboratory observations seemed to indicate that the patient herein described was afflicted with the type of polyneuritis known as the Guillain-Barré syndrome. To be sure, the rapid onset with elevated temperature, meningeal irritation and sudden motor impairment is characteristic of poliomyelitis, but it is also commonly observed in children affected by "infectious polyneuritis." At the paralytic stage, the patient showed a severe motor involvement, which was diffuse, bilateral and symmetric in distribution as observed in the Guillain-Barré syndrome, in contrast to the localized and asymmetric distribution seen in acute anterior poliomyelitis. Moreover, in each extremity the distal muscles were less involved than the proximal ones, a differential criterion in favor of infectious polyneuritis and against poliomyelitis (DeSanctis and Green [2]). In accordance wiith the diffuse character of the motor impairment, the muscular atrophy and the absence of reflexes were also diffuse. Respiratory failure was present: This is often seen in poliomyelitis, but its occurrence in "infectious polyneuritis" is also frequent, as evidenced by the material published by Foster, Brown and Merritt,[3] in which it was reported that 13 patients of 26 showed signs

2. DeSanctis, A. G., and Green, M.: Acute Infectious Polyneuritis: A Diagnostic Problem During a Poliomyelitis Epidemic, J. A. M. A. **118**:1445 (April 1) 1942.

3. Foster, F. M.; Brown, M., and Merritt, H. H.: Polyneuritis with Facial Diplegia: A Clinical Study, New England J. Med. **225**:51, 1941.

of respiratory failure. Of considerable interest is the presence of optic neuritis; this sign is doubtless extremely rare in poliomyelitis (4 cases cited by Wilson [4]) while it has been repeatedly reported in cases of the Guillain-Barré syndrome (van Gehuchten,[5] Gilpin, Moersch and Kernohan,[6] Roseman and Aring [7] and Dumolard, Schousboé and Badaroux.[8] Apart from the optic nerve, involvement of cranial nerves and particularly of the seventh was not observed. Although a significant sign of the Guillain-Barré syndrome, paralysis of the facial nerve is far from being a constant manifestation, since it is found only in about one third of the patients.

The results of repeated examinations of the spinal fluid were strikingly characteristic of the Guillain-Barré syndrome. As is well known, the "albuminocytologic dissociation" is a cardinal constituent of the syndrome. In all examinations the number of cells was normal, while the total proteins were always above 100 mg. per hundred cubic centimeters. On one occasion the figure 1,200 mg. per hundred cubic centimeters was observed. It should be noted that in poliomyelitis the amount of total protein may be increased (Meyer [9]), especially during the first two weeks, but such high figures as those observed in the present case have not been previously reported. In cases of the Guillain-Barré syndrome, on the other hand, still higher amounts have been found (e. g. 3,000 mg. [van Bogaert [10]]). Moreover, the number of cells is increased and usually conspicuously so in poliomyelitis, while in the present case a normal number was found.

On the basis, therefore, of the clinical manifestations and the laboratory observations, the diagnosis of Guillain-Barré syndrome appeared justified.

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4. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, William Wood & Company, 1940, vol. 1, p. 237.

5. van Gehuchten, P.: Un cas de poly-radiculonévrite avec dissociation albumino-cytologique et oedème de la papille, J. belge de neurol. et de psychiat. **38**: 212, 1938.

6. Gilpin, F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: A Clinical and Pathologic Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis, Arch. Neurol. & Psychiat. **35**:937 (May) 1936.

7. Roseman, E., and Aring, C. D.: Infectious Polyneuritis, Medicine **20**:463, 1941.

8. Dumolard, S. C.; Schousboé, F., and Badaroux: Polyradiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire et névrite optique, Rev. d'oto-neuro-opht. **15**:26, 1937.

9. Meyer, R.: Le diagnostic précoce de la maladie de Heine-Medin, Rev. franç. de pédiat. **12**:756, 1936.

10. van Bogaert, L.; Phillips, F.; Rademecker, J.; Rademecker, M. A., and Verschraegen, T.: Essai sur un groupe épidémique de cas de poly-radiculonévrite avec dissociation albumino-cytologique du liquide céphalo-rachidien (type de Guillain et Barré), chez l'enfant et chez l'adulte, J. belge de neurol. et de psychiat. **38**:151, 1938.

The pathologic examination leaves little doubt as to the diagnosis of acute anterior poliomyelitis. The localization of the process to the anterior horns of the spinal cord and the morphologic features of the lesions were characteristic of poliomyelitis. The destruction of nerve cells and myelin was generally predominant over the vascular component; this perhaps should be ascribed to the "tempo" of the lesions more than to a special characteristic of the process. Of considerable interest was the almost complete absence of meningeal infiltration, a condition which perhaps accounted for the low number of cells in the spinal fluid. The changes in the peripheral nerves appeared to represent chiefly a secondary reaction to injury of the anterior horn.

The present observation brings to the fore the difficulties in differentiating clinically between poliomyelitis and the Guillain-Barré syndrome in children. Differential criteria have been mentioned in numerous publications and concern mainly the mode of onset, the distribution of the paralysis and the laboratory observations. However, in cases in which the poliomyelitic process is diffuse, as in that of the patient here described, the type of distribution of the paralysis is an unreliable criterion. Moreover, in children the mode of onset is the same in the two diseases. The albuminocytologic dissociation, the importance of which has been stressed many a time, may be found also in poliomyelitis, as evidenced by the present observation. According to Guillain and the majority of the French investigators, the favorable outcome is an outstanding feature of "infectious polyneuritis" and an important differential sign from poliomyelitis. However, recent statistics point out the occurrence of a high rate of mortality in polyneuritis (18.8 per cent in the series of Roseman and Aring [7] and 42 per cent in that of Foster, Brown and Merritt),[8] which indicates, perhaps, an increase in virulence of the disease in late years. On the other hand, complete recovery following an attack of poliomyelitis is frequently observed, especially during certain epidemics. It has been claimed, finally, that poliomyelitis may occur in epidemics while cases of the Guillain-Barré syndrome are sporadic. However, a small epidemic of typical Guillain-Barré syndrome in children has been reported recently by van Bogaert and co-workers.[10]

In a certain number of cases, in conclusion, as already pointed out by other investigators (Dereux,[11] Giraud and Boudouresques [12] and Cohen [13]), the differential diagnosis between the Guillain-Barré syndrome and acute poliomyelitis is clinically impossible.

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11. Dereux, J.: A propos d'un cas anormale de poliomyélite antérieur aiguë chez un enfant, J. belge de neurol. et de psychiat. **38**:228, 1938.

12. Giraud, P., and Boudouresques, J.: Radiculonévrite avec dissociation albumino-cytologique du liquide céphalo-rachidien (syndrome de Guillain et Barré) chez l'enfant, J. belge de neurol. et de psychiat. **38**:256, 1938.

13. Cohen, C.: A propos de trois enfants présentant certain charactères du syndrome de Guillain-Barré, J. belge de neurol. et de psychiat. **38**:307, 1938.

The observation here reported, moreover, raises the problem as to whether the two diseases are distinct entities or different clinical manifestations of the same agent. When, as observed in the present case, a pathologically confirmed poliomyelitic process manifests itself with the clinical symptoms and signs of the Guillain-Barré syndrome, the conclusion appears justified, perhaps, that other cases of the latter disease are actually instances of anterior poliomyelitis with favorable outcome. A similar hypothesis has been advanced by Cohen,[13] who suggested that an attenuated or modified poliomyelitic virus is responsible for the Guillain-Barré syndrome. In this connection it is pertinent to cite the epidemiologic observations of Kissel[14]: This author reported an epidemic in a small village in which 5 typical cases of anterior poliomyelitis were preceded by 8 cases of facial palsy similar in their clinical characteristics to the type of Guillain-Barré syndrome described by van Bogaert and Maere[15] as "cranial forms."

Since differentiation based on clinical symptoms, observations of the cerebrospinal fluid and final outcome are open to question, the problem of the relation between anterior poliomyelitis and the Guillain-Barré syndrome can be approached only from the etiologic point of view by attempting to isolate poliomyelitic virus or another virus from patients with "infectious polyneuritis."

SUMMARY

The case of a patient is described who showed the clinical manifestations and laboratory findings that are considered typical of the Guillain-Barré syndrome and in whom post mortem the disease appeared to be acute anterior poliomyelitis. On the basis of these observations and the pertinent data of the literature, the difficulty in differentiating clinically between the two diseases is pointed out and the hypothesis is advanced that a number of cases of the Guillain-Barré syndrome may actually be instances of anterior poliomyelitis with favorable outcome.

14. Kissel, P.: Epidémie de paralysies faciales d'origine poliomyélitique, Rev. neurol. **19**:725, 1938.

15. van Bogaert, L., and Maere, M.: Les poly-radiculonévrites craniennes, bilaterales. Forme craniennes des polyradiculonévrites du type Guillain et Barré, J. belge de neurol. et de psychiat. **38**:275, 1938.

HYPOPLASIA OF THE MANDIBLE

REPORT OF A CASE, WITH A RÉSUMÉ OF THE LITERATURE AND SUGGESTIONS FOR A MODIFIED FORM OF TREATMENT

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Hypoplasia of the mandible, micrognathia, hypomicrognathia, bird face and the Pierre Robin syndrome are synonyms for a condition characterized by an abnormally small and retruded lower jaw. This pathologic complex has its origin in an extreme hypoplasia of the mandible and is regularly accompanied by cleft palate, a foreshortening of the genioglossal muscles and glossoptosis, resulting in blocking of the air and food passages. Clinically, the condition is characterized by cyanosis and dyspnea, which are more pronounced during feedings.[1] Because feedings are often difficult or impossible, dehydration and cachexia are usually present.

Although this is a rare syndrome, it probably occurs more often than is suspected and the afflicted infant dies of asphyxia or starvation before the condition is recognized. Even after recognition of the pathologic state, furthermore, a poor prognosis is given and treatment frequently inadequate, though it could be simple and effective.

Congenital syphilis, hereditary dystrophy from alcoholism and various infections are among many causes cited for this unusual deformity.[2] Malnutrition of the embryo is considered a factor in many cases; some authors contend that the deformity is purely a hereditary condition. After normal retrusion of the lower jaw during the fourth and fifth months of intrauterine life, rapid growth permits it to equal the size of the maxilla by birth. It is thought, however, that various inhibitory factors may retard or prevent this rapid growth.

We are proponents of Davis and Dunn's theory,[3] that in utero the weight of the fetal body may be forced on the vertex of the head and

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1. Lapage, C. P.: Micrognathia in the Newborn, Lancet **1**:323-324 (Feb. 6) 1937.

2. Ivy, R. H.: Congenital and Acquired Defects and Deformities of Face and Jaws: Review of Literature for 1936, Internat. Abstr. Surg. **64**:433-442, 1937; in Surg., Gynec. & Obst., May 1937.

3. Davis, A. D., and Dunn, R.: Micrognathia: Suggested Treatment for Correction in Early Infancy, Am. J. Dis. Child. **45**:799-806 (April) 1933.

that in such a position of flexion there is a back pressure on the mandible caused by its forceful contact with the sternum. If this occurs before the mandible is calcified completely, the bone may be forced posteriorly, causing the ramus-corpus angle of the mandible to become a right angle or less instead of the normal obtuse angle. On this theory, one may reason further that such a pressure prevents fusion of the horizontal plates of the palate and causes a cleft. Additional inference easily accounts for the displacement of the tongue.[4]

The ramus-corpus angle of the mandible being a right angle or less causes retrusion and forces the structures in the floor of the mouth posteriorly. The genioglossal muscles, which afford traction on the tongue and keep it forward, may be absent, as reported of sheep with analogous deformities of the lower jaw, or they may be present but unable to exert traction, as insertion is at the retruded symphysis menti.[5] In either case, the tongue falls into the oropharynx, where the flow of air is obstructed, especially when the mouth is closed. The flow of air is obstructed further if the base of the tongue presses on the epiglottis and effects a closure of the glottis. The tongue in the oropharynx also impairs deglutition because of the decrease in the anterior-posterior diameter of the pharynx.[6] Because a cleft palate of varying degree is usually present, the feeding problem is even more difficult and this difficulty hastens dehydration and cachexia.[7]

The question concerning the mentality of infants with this deformity has arisen. Some embryologists believe that deformities of the lower jaws are accompanied by defective development of the forebrain and hindbrain.[5] Although children with retruded chins resemble idiots, we have found no mention of lowered mentality in the literature reviewed. In later life these children may have a slumped appearance and be mentally dull, but it may be questioned whether this is congenital. It is plausible to assume that it may be due to the slow start in life these children usually have. Also, mental dulness may be the result of cerebral ischemia due to periods of frequent and prolonged cyanosis.

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4. Thoma, K. H.: Principal Factors Controlling Development of Mandible and Maxilla, Am. J. Orthodontics **24**:171-179 (Feb.) 1938. Janse, H. M.: Macroglossia with Associated Micrognathia Causing Respiratory Difficulty, Ann. Otol., Rhin. & Laryng. **39**:99-103 (March) 1930. Weisengreen, H. H., and Sorsky, E. D.: Congenital Hypoplasia of Mandible, J. Pediat. **16**:482-486 (April) 1940.

5. Gladstone, R. J., and Wakeley, C. P. G.: Defective Development of the Mandibular Arch: The Etiology of Arrested Development and Inquiry into the Question of the Inheritance of Congenital Defects, J. Anat. **57**:149-167, 1922-1923.

6. (*a*) Charles, S. W.: Development of Mandible, Internat. J. Orthodontia **22**:674-684 (July) 1936. (*b*) Robin, P.: Glossoptosis Due to Atresia and Hypertrophy of Mandible, Am. J. Dis. Child. **48**:541-547 (Sept.) 1934.

7. Eley, R. C., and Farber, S.: Hypoplasia of the Mandible (Micrognathy) as a Cause of Cyanotic Attacks in the Newly Born Infant: Report of Four Cases, Am. J. Dis. Child. **39**:1167-1175 (June) 1930.

REPORT OF CASE

A girl was admitted to the pediatric service of Dr. Stanley Gibson at St. Luke's Hospital on Sept. 26, 1941. She had been born three weeks previously to an 18 year old primiparous mother, who stated that the period of gestation and the delivery were uncomplicated. The infant weighed 7 pounds 8 ounces (3,402 Gm.) at birth but had steadily lost weight and on admission weighed 5 pounds ½ ounce (2,282 Gm.). The mother complained that the child had had difficulty in breathing and attacks of "blueness" since birth, which were particularly pronounced during feedings.

Photographs of the patient: *A*, before treatment was begun; *B*, with the corrective brace in place; *C*, after completion of treatment.

Examinations revealed an emaciated infant with deep cyanosis and dyspnea. The palpebrae were swollen and edematous; the conjunctiva was inflamed, and there was a left internal strabismus. Two lower incisor teeth were present. The tongue was of a globular shape and located posteriorly in the oral cavity. A cleft palate was present. The lower jaw was retruded (fig., *A*) but could be forced forward by pressure at the posterior part of the ramus.

The thorax, in violent respiratory motions constantly, was normal, as were the heart and lungs, except that breath sounds were audible only once in every four or five respiratory excursions.

Laboratory reports showed a moderate anemia, but the results of urinalysis and the serologic reactions of the blood were normal.

Because of the respiratory difficulty, the infant was placed prone in an incubator with a constant supply of oxygen. A small pillow was placed under the upper

part of the thorax. Respiratory difficulty ceased, and the cyanosis disappeared. Gavage every four hours was instituted.

After the patient gained weight and the respiratory difficulty was controlled by posture, a small brace (fig., *B*), to be described, was made, which allowed the infant to sit up or to rest supine without respiratory difficulty. At the time of writing, the child is a little over 1 year old. The cleft palate has been repaired successfully. She is spoon fed, and, though her performance is slightly below the 1 year old level, she is developing well (fig., *C*).

TREATMENT

Many devices have been used in the treatment of this condition, but only a few deserve mention.[8] Obviously, surgical advancement of the jaw is not feasible for infants; so treatment is directed along conservative lines, all of which merely aid nature to allow the development of the lower jaw gradually to equal or overtake the growth of the maxilla. Nature accomplishes this usually in six or eight months. The mandible grows posterior to the region of the third molar and is influenced by muscular action and increase in collateral circulation.[9] It grows to normal facial proportions even when there is anodontia or when an entire set of teeth remains unerupted or impacted. Early acquired ankylosis with its concomitant atrophy of the muscle is probably the only condition in which the mandible fails to grow properly. All this proves that muscle action accounts for the most of mandibular growth. Until muscle action has been established, therefore, the treatment is directed toward artificial means of keeping the jaw forward and aiding growth. Robin [10] first advocated orthostatic feedings, in which the child is forced to suckle as do mammals, reaching its head upward and forward while prone. This tends to force the lower jaw forward in an effort to grasp the nipple. With excellent results Davis and Dunn employed the same principle.[3] A metal form which fits the upper lip and which, in turn, is attached to the nursing bottle by means of an adjustable attachment permits the gradual lengthening of the distance between the nipple and the lips and thus forces the jaw forward. Callister [11] employed a form of skeletal traction with equally good results. A jury-mast, frequently used in the treatment of a fractured cervical vertebra, was attached to the body of the infant and from behind a flat half ring was attached to the mast in

8. McCoy, J. D.: Factors Which Control Treatment of Dwarfed Mandible, Am. J. Orthodontics **25**: 850-864 (Sept.) 1939.

9. Scott, E. J.: Experimental Study in Growth of the Mandible: Preliminary Report, Am. J. Orthodontics **24**: 925-934 (Oct.) 1938.

10. Schwartz, L.: Ateliosis of Mandibular Arch: Clinical Comment on Glossoptosis, Syndrome of Pierre Robin, Arch. Otolaryng. **31**:491-501 (March) 1940. Robin.[6b]

11. Callister, A. C.: Hypoplasia of Mandible with Cleft Palate: Treatment in Early Infancy by Skeletal Traction, Am. J. Dis. Child. **53**:1057-1059 (April) 1937.

such a way that the free end could be placed directly in front of the mandible. By means of a silver wire through the mandible at the symphysis, which was attached by a spiral spring to the ring, enough traction was exerted to pull the jaw forward.

In our experience, posture is an effective method of treatment. The child can be placed in a prone position with the chest elevated by means of a small pillow so that only the forehead and the chest touch the mattress and the lower jaw falls forward by its own weight. This position promptly relieves the cyanosis, dyspnea and choking. As this position obviously cannot be maintained at all times, a simple metal attachment for the head was devised (fig., *B*). It consists of a metal head ring to the sides of which metal bars are attached. These extend downward and slightly forward. At the free ends of the drop bars felt pads impinge between posterior edge of the rami of the mandible and the external auditory meatuses. This mechanism presses the jaw forward.

SUMMARY

A case of micrognathia in a newborn infant is reported. A résumé of the literature is presented together with a modified form of treatment and suggestions as to the care of infants with this deformity.

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Progress in Pediatrics

ACUTE LYMPHATIC LEUKEMIA IN CHILDHOOD

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Acute lymphatic leukemia is not infrequently encountered in childhood and presents little difficulty in differential diagnosis when the typical clinical and hematologic features are present. In many instances, however, atypical manifestations may cloud the picture to the extent that the diagnosis becomes more difficult. This is particularly true when the total leukocyte count is not significantly elevated and the differential formula does not present the usual preponderance of immature cells. It is now recognized that these instances of so-called "aleukemic" or "subleukemic" forms of lymphatic leukemia are not rare but constitute a considerable proportion of the total number of cases. In order to compare the incidence, course and manifestations of this aleukemic form with those of the more typical variety, with an elevated leukocyte count, we have reviewed the cases of 61 consecutive patients with acute lymphatic leukemia admitted to the pediatric service of the University Hospitals. Since all children admitted to this service are under 16 years of age, this report is confined to leukemia in that age group.

Lymphatic leukemia in childhood is almost always of the acute variety,[1] and, although occasionally the chronic form of the disease may be encountered, it is rare, and the extreme chronicity so frequent in adults is not observed. In the present series there was 1 patient who lived for fourteen months after the onset of symptoms. This was the nearest approach to the chronic form of the disease which we observed.

Previous reports have emphasized the greater incidence of leukemia in males as compared with females [2] and the greater incidence in younger

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1. Spigel, H. A.: Leukemias of Infancy and Early Childhood, Arch. Pediat. **55**:7, 1938. Cooke, J. V.: Acute Leukemia in Children, J. A. M. A. **101**:432 (Aug. 5) 1933.

2. Warren, S. L.: Acute Leukemia: A Review of the Literature and of Twenty-Eight New Cases, Am. J. M. Sc. **178**:490, 1929. Ward, G.: The Infective Theory of Acute Leukemia, Brit. J. Child. Dis. **14**:10, 1917. Mills, S. D.: Acute Lymphatic Leucemia in Childhood, J. Pediat. **6**:634, 1935.

children as compared with those over 5 years of age.[3] The age of the children under our observation varied from 3½ months to 15 years; the distribution of patients in 5 year age groups is shown in table 1, and the age distribution by years is graphically portrayed in chart 1. It is to be noted that the incidence was higher in the younger age groups and declined with advancing years. Three afflicted children under 1 year of age were observed. The patients were 3½, 5 and 11 months of age

TABLE 1.—*Age Incidence in Five Year Groups*

Age	Patients	Boys	Girls
0- 5	26	17	9
6-10	20	15	5
11-15	15	9	6

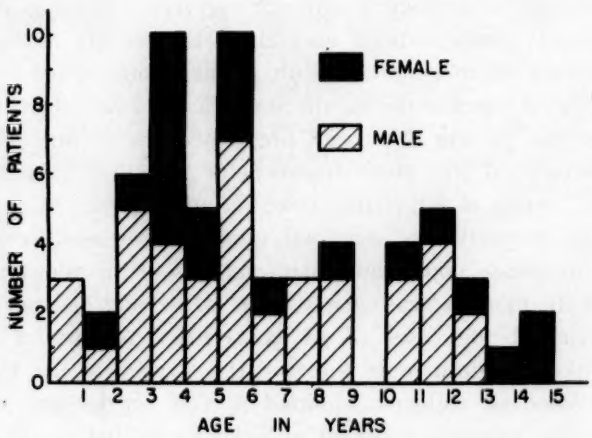

Chart 1.—Age distribution by years.

respectively, and it is of interest to note that in all of them the disease presented an acute onset and a rapid course. A higher incidence of the disease in males was encountered in this series of patients, 41, or 67.2 per cent, being boys and 20, or 32.8 per cent, being girls. This difference in sex incidence was more pronounced in the younger patients, and it will be noted that the 3 patients above 13 years of age were all girls.

The total leukocyte counts for this series of patients at the time of their admission to the hospital ranged from 1,900 to 1,000,000 per cubic millimeter. For the purposes of this paper patients with a leukocyte count of 12,000 or less were considered to be in an aleukemic stage. With this figure as an empiric dividing line it was found that there were 32 in the leukemic and 27 in the aleukemic phase at the time of their

3. Ramsey, G. W. S.: Leukemia in Infancy and Early Life, Arch. Dis. Childhood **2**:119, 1927.

admission to the hospital. For 2 patients the distinction could not be made: one was moribund at the time of admission and died before a leukocyte count was done, and for a second patient only a blood smear was obtained before death.

Three of the 27 patients admitted to the hospital in the aleukemic phase subsequently changed to the leukemic state, and 4 of the 32 patients admitted in the leukemic stage later had an aleukemic phase. None of these 7 patients had an extremely high or low count at any time, the greatest change being in a patient who had 5,450 leukocytes on admission but terminally had a count of 63,300. In no patient with a count of over 30,000 did an aleukemic state develop, nor did any patient with a count below 5,000 reach the leukemic phase while under our observation.

A leukemic blood picture was more frequent than an aleukemic one in the younger patients, as is shown in table 2. Of the 26 patients less than 6 years of age, 17 were leukemic and 8 were aleukemic. The remaining patient was one of the 2 for whom the type was not determined.

TABLE 2.—*Frequency of Leukemic and Aleukemic Forms in Different Age Groups*

Age	Leukemic Form	Aleukemic Form
0- 5	17	8
6-10	8	12
10-15	7	7

All 3 of the patients under 1 year of age had elevated leukocyte counts. In children from 6 to 10 years of age there were more aleukemic than leukemic forms, and of children from 11 to 15 years equal numbers had the two types.

The lowest total leukocyte counts encountered were 1,500 (2 patients) and 1,900, and there were 14 patients with counts between 2,000 and 5,000. In the presence of these low counts the percentage of lymphocytes remained high, comprising from 60 to 98 per cent of the cells on the smear. The average percentage of lymphocytes for the group of 27 aleukemic patients was 85. In these patients with the lower leukocyte counts the predominant cell was the mature lymphocyte, and, although immature lymphocytes were present, they made up a smaller percentage of the cells than in the leukemic form of the disease.

The highest total leukocyte count encountered was 1,000,000, and the next highest were 420,000 and 350,000. There were 3 patients with between 200,000 and 300,000 leukocytes, 4 patients having between 100,000 and 200,000 and 4 between 50,000 and 100,000, with the remainder of the 32 leukemic patients having counts below 50,000. The average percentage of lymphocytes encountered in this group was 89, as compared with 85 in the aleukemic group. In patients with extremely

elevated leukocyte counts the immature lymphocyte was the predominant cell encountered on the smear, whereas immature cells were less frequent in the aleukemic phase. With careful searching, however, examples of immature lymphocytes will be found in all cases. Not all of these immature cells were typical large lymphoblasts many being small and but little larger than the mature lymphocyte. The evidences of immaturity in these cells consisted of an evenly distributed threadlike or cordlike arrangement of the chromatin of the nucleus, giving it a light-staining bland appearance, the presence of nucleoli, a somewhat irregular shaped nucleus and rather abundant cytoplasm. Such cells on a thick smear or with a hasty and careless examination may be easily mistaken for an adult cell. With a low leukocyte count and a preponderance of these relatively small lymphocytes, the blood smear of a patient with this form of the disease may be easily confused with that of a person with aplastic anemia.

An anemia of varying degree always accompanies lymphatic leukemia. In many instances the fall in the values for hemoglobin and erythrocytes is extremely rapid, and the predominant symptoms of the disease may be those of the associated anemia. The erythrocytes are typically hypochromic, with little alteration in their size and shape. Nucleated forms are not infrequent, being particularly numerous in some cases, and reticulocytes are present in varying numbers as an indication of regenerative power of the bone marrow. In comparing the erythrocyte counts of patients with the leukemic form of the disease and of patients with the aleukemic form it was found that the average for the leukemic group was 2,640,000, while for the aleukemic group it was 1,940,000. The lower erythrocyte count of the aleukemic patients is probably due to the more chronic course and the longer duration of the disease in these patients. In both the leukemic and the aleukemic type the erythrocyte count frequently dropped rapidly while the patient was under observation; hence counts of from 500,000 to 600,000 were not uncommon in the terminal stages of the disease. The administration of transfusions had but a slight transient effect on the anemia, and the subjective improvement was also of short duration. In the more acute and rapidly progressive forms of the disease the beneficial effects of transfusions were even less evident.

Secondary thrombopenic purpura is a common complication of acute leukemia and is characterized from a laboratory standpoint by the following features: (1) diminished platelets, (2) prolonged bleeding time but a normal coagulation time, (3) nonretractable clot and (4) a positive constrictor, or Rumpel-Leede, test. Of the 36 patients on whom these tests were carried out, there were 31 for whom the findings were indicative of thrombopenic purpura. In the aleukemic group the four features

were present in 18 of 22 patients, or 81.8 per cent, while in the leukemic group 13 of 14 had positive results, or 92.8 per cent. These observations show the extremely high incidence of thrombopenic purpura in acute lymphatic leukemia and explain the frequency with which hemorrhagic manifestations appear in the clinical picture. A similarly high incidence is also encountered in the acute type of myelogenous leukemia; therefore this finding is of no value in the differential diagnosis of lymphatic leukemia.

The aleukemic form of acute lymphatic leukemia may easily be mistaken for aplastic anemia, since it is characterized by a severe progressive anemia, a low total leukocyte count, with a relative lymphocytosis frequently characterized by but slight evidence of immaturity of the cells and an almost complete absence of neutrophils, and a low platelet count, with the other clinical and laboratory evidences of thrombopenic purpura. Such a picture is similar to that of aplastic anemia. In leukemia, however, there is a generalized, although possibly slight, lymphadenopathy with splenomegaly, which is not present in aplastic anemia. The reticulocyte count is usually higher, and a careful differential count will reveal evidences of immaturity of the lymphocytes, conditions which are not found in aplastic anemia. A sternal puncture or biopsy or biopsy of a lymph node should establish the diagnosis without question. In our experience, aplastic anemia in children is rare and is far less frequently encountered than is lymphatic leukemia.

In cases in which a postmortem examination was made, the usual histologic picture of lymphatic leukemia was found. The infiltration of the organs and tissues by the leukemic cells was present, with extensive involvement of the liver and spleen and with infiltration of the bone marrow to varying degrees. The architecture of the lymph nodes was destroyed by the overgrowth of the lymphoid cells, and the predominant cell was the large immature lymphoblast. The degree of infiltration varied from one patient to another, and in the same patient not all the lymph nodes were involved to the same extent. Differences in the histologic picture could not be detected between patients showing a leukemic and those with an aleukemic peripheral blood picture either in respect to the extent of involvement or in regard to the degree of immaturity of the cells. Necropsy in 1 case in which the patient was aleukemic in the initial phase but had a terminal leukocyte count of 63,300 showed no differences from the other patients. No explanation can be offered for the differences in the total leukocyte counts.

CLINICAL FEATURES

In respect to the onset, course and symptoms of the disease there are no essential differences between the patients with an elevated leuko-

cyte count and those with a normal or low total leukocyte count. In chart 2 the frequency of the various complaints are shown as they were given by the patient or parents at the time of admission to the hospital, and in chart 3 are shown the findings on examination, both being separated into the leukemic and the aleukemic group. It was noted that fatigue and malaise were among the entrance complaints of 17 of the patients with an elevated leukocyte count but of only 9 of those in an aleukemic state. These symptoms were present to some extent in all of the patients, and the difference in the two groups is probably a result of inaccurate taking of the history rather than a true difference in symp-

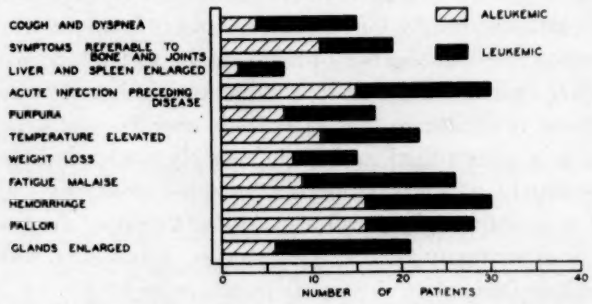

Chart 2.—Complaints at the time of admission to the hospital.

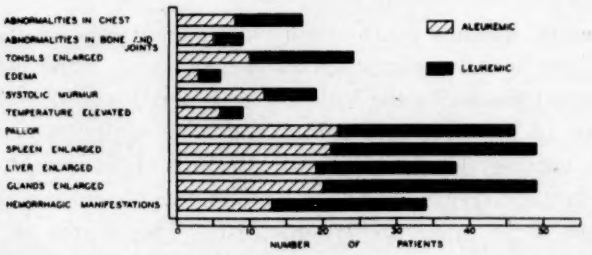

Chart 3.—Physical findings at the time of admission to the hospital.

tomatology. Pallor and loss of weight were common in the disease in both forms, although emaciation and extreme loss of weight are not to be expected. Enlarged lymph nodes were noted before admission to the hospital in 15 of the patients with elevated leukocyte counts but in only 5 of the aleukemic patients, and it is to be noted in the chart that lymphadenopathy was found to be more prevalent and more extensive in the leukemic patients. It seemed, therefore, that enlargement of the nodes was a more prominent feature of those cases in which the circulating lymphocytes were increased than of those in which the total leukocyte count was normal or low, although the reason for this is not apparent

from the histologic picture. The nodes were discrete and movable and as a rule were not tender and did not suppurate. They were softer in consistency than the nodes involved by Hodgkin's disease or by metastatic malignant neoplasms. An enlargement of the liver and spleen was seldom detected prior to admission to the hospital, although in 47 children the spleen was enlarged at the time of admission. This too was more prominent and more frequent in patients with a leukemic blood picture. The liver was enlarged in 39 of the 61 patients, and this also was more common in those with an elevated leukocyte count. Hypertrophied tonsillar tissue was found in 24 of the 61 children. This incidence was no greater than was found among the children admitted routinely to the pediatric service; hence the tonsils do not seem to be particularly affected by the leukemic process.

Difficult breathing and cough were noted in 15 patients prior to admission, and in 11 of these a leukemic blood picture was present. On roentgenographic examination of the chest a widened mediastinum due to enlarged mediastinal nodes was found in 17 cases. The cough which is produced by mediastinal obstruction may be a particularly distressing feature in certain patients, as, for example, in 1 child who was brought to the hospital because of a chronic nonproductive cough of four months' duration associated with shortness of breath. The cough was dry and rasping and was made worse by recumbency. The superficial veins of the anterior thoracic wall and neck were prominent, and physical examination revealed signs of a pleural effusion on the left. This was confirmed by roentgenograms, which also showed a greatly widened mediastinum. Roentgen therapy to the mediastinum resulted in subsidence of the dyspnea and regression in the size of the mediastinal mass, and, although death occurred three months after the first hospital admission, there had been no recurrence of the cough or dyspnea after therapy. In addition to the patients showing a widened mediastinum, there were 4 patients who had a pleural effusion, and in 5 there were actual infiltration and invasion of the pulmonary tissue.

One interesting feature of leukemia in these children was the frequency with which the onset followed closely an acute infectious process of some type. Such a history was obtained in 30 cases. There are several interpretations that can be placed on this feature. There is still a diversity of opinion as to the cause of acute lymphatic leukemia, and those who hold it to be infectious in origin may point to the preceding infection as evidence to support their contention. Such an interpretation is not well founded, however, since acute infections of various types are common in children of this age group and may be purely coincidental. The leukemia may have been present but unrecognized at the time of the infection and may so have lowered the resistance

of the child that he was particularly susceptible to an infectious process. The incidence of acute infections is particularly high in the late stages of leukemia in any age group because of this increased susceptibility. It is also possible that an unrecognized leukemia may have been present and the superimposed infection may have aggravated the symptoms to the point that they became apparent, or the child may have been under closer observation during and after the acute infection, so that the features of leukemia were recognized at that time. Regardless of the interpretation placed on the association of leukemia and infection, it does not lend definite support to an infectious origin of leukemia. Fever is commonly observed in acute leukemia and was found in 22 of these patients, but it is undoubtedly present at some time in the course of the disease in all patients, even in the absence of infection.

Hemorrhage of some degree was noted in 30 of the patients prior to their admission to the hospital and purpura was noted in 17 patients. A far greater number displayed hemorrhagic manifestations later in the course of the disease. Many of the patients were admitted to the hospital only for confirmation of the diagnosis and were not followed throughout the entire course of the illness; hence the exact number ultimately evincing hemorrhagic manifestations cannot be determined from this group. However, in those followed to the terminal stage hemorrhage was invariably evident in some manner. The most frequent sites of bleeding were the nose and gums, but in the more severe forms hemorrhages occurred from other sites as well. In 1 of the older girls of the group a prolonged menstrual period with an exceedingly profuse discharge was the initial symptom of the disease. A diminution in the blood platelets is particularly common in the terminal stage of lymphatic leukemia, and associated with this are the other laboratory features of thrombopenic purpura; the hemorrhagic tendencies are on this basis. A severe progressive anemia is a feature of acute leukemia, and this is made worse by the loss of large amounts of blood.

Pains referable to the bones or joints are not infrequent in leukemia of this type [4] and were noted in 19 of the 61 cases, being somewhat more frequent in patients with the aleukemic type of the disease. Such symptoms occasionally occur in an adult with an acute form of lymphatic leukemia but are far more common in children. When the clinical and hematologic features are otherwise typical of leukemia, such a picture offers little difficulty in diagnosis; but when articular manifestations

4. Smith, C. H.: Leucemia in Childhood with Onset Simulating Rheumatic Disease, J. Pediat. **7**:390, 1935. Abt, A. F.: The Diagnosis of Leukemia in Childhood, Pennsylvania M. J. **38**:389, 1935. Jackson, H.: The Protean Character of the Leukemias and of the Leukemoid States, New England J. Med. **220**:175, 1939.

occur early in a patient with an aleukemic phase of the disease, the condition may be easily mistaken for rheumatic fever, particularly if the pulse rate is rapid and a hemic cardiac murmur is present. At other times the disease is mistaken for infectious arthritis, especially if the joints are red and swollen and a fever is present. Pains in the joints were present in the patient of this series in whom the condition presented the most chronic course. His first manifestation of the illness was lameness and awkwardness on walking, which appeared after an attack of coryza. A diagnosis of infectious arthritis was made when he was first examined, although his erythrocyte count was 1,980,000 and the leukocyte count was 2,600 with 63 per cent lymphocytes. His fever, articular pain and muscular atrophy persisted, but the subsequent appearance of enlarged lymph nodes and splenomegaly led to more careful hematologic examinations, which established the diagnosis of leukemia. Mediastinal enlargement eventually appeared, and hemorrhagic manifestations developed shortly before death.

Roentgenologic evidence of involvement of the bones may be found in certain cases,[5] although there is no correlation between this and the presence of pain. The roentgenologic features are not of a type which is pathognomonic of leukemia and thus are variable in their appearance. These changes are more frequently found in the bones containing hemopoietic marrow and may be confined to the periosteum. The lesions may be either osteoclastic or osteosclerotic, but the one most frequently found is a narrow transverse zone of lessened density proximal to the metaphysis of long bones. In the skull and pelvis the most common lesion is a generalized osteoporosis which is irregular and mottled in its appearance.

The course of the leukemia was acute and rapidly progressive except in 1 patient who lived for fourteen months after the onset of symptoms, and even this is an acute course as compared with the type of disease commonly encountered in adults. The average duration of life from the onset of symptoms until death of children for whom the time of death was known was eighteen weeks. This duration of life was the same for the leukemic and the aleukemic patients, being seventeen and nine-tenths weeks for the aleukemic patients and seventeen and seven-tenths weeks for the leukemic. The length of life varied from one to fifty-six weeks for children with the aleukemic form and from four to twenty-eight weeks for those with the leukemic form.

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5. Snelling, C. E.; Brown, A., and Erb, I. H.: Bone Changes in Leukemia: I. Clinical and Roentgenological; II. Pathology, Arch. Dis. Childhood **9**:315, 1934. Baty, J. M., and Vogt, E. C.: Bone Changes of Leukemia in Children, Am. J. Roentgenol. **34**:310, 1935. Craver, L. F., and Copeland, M. M.: Changes of the Bones in the Leukemias, Arch. Surg. **30**:639 (April) 1935.

The cause of death of 9 of the 18 patients who died while under observation in the hospital was complications or superimposed infections. One child died of respiratory failure preceded by extreme cyanosis from mediastinal obstruction. There were 4 who succumbed to lobar pneumonia and 1 to otitis media. Six children died as a result of profuse uncontrollable hemorrhage and 1 with a convulsion resulting from cerebral hemorrhage. Two patients were moribund at the time of their admission to the hospital and died soon thereafter, and 3 died from the progressive weakness and anemia associated with the disease.

There is little that can be said regarding the treatment of these patients. High voltage roentgen therapy was tried for 15 children with enlarged mediastinal nodes and for children in whom pressure manifestations from enlarged nodes were present. Such therapy relieved the pressure symptoms and consequently made the patient more comfortable. In this way it prolonged life. Roentgen therapy to the liver, spleen or nodes for children without pressure symptoms did not improve the patient's condition nor prolong life. In fact, in some instances in which this was tried it apparently made the condition worse by greatly increasing the already elevated metabolic rate and hastened the fatal outcome. We believe, therefore, that roentgen therapy should be used only for relief of pressure symptoms or for relief of localized pain and that such therapy is contraindicated in the absence of these features.

Transfusions were administered to 34 patients in this series. There was symptomatic improvement with this procedure, and the patient felt better for a short time after the blood was administered. The total amount of blood given by transfusion varied from 250 to 10,000 cc. Although temporary improvement resulted from the transfusions, we could find no evidence that the administration of blood prolonged life, the duration of life being no greater for the group receiving multiple transfusions than for those who received no blood.

SUMMARY AND CONCLUSIONS

The aleukemic and the leukemic form of acute lymphatic leukemia in childhood occur with about equal frequency. They present no essential differences in their clinical picture except that the leukemic form tends to pursue a somewhat more acute course and to produce more pronounced lymphoid hyperplasia.

The aleukemic form is more difficult of diagnosis and more easily mistaken for aplastic anemia, arthritis or an acute infectious process.

Roentgen therapy of acute lymphatic leukemia is effective in alleviating pressure symptoms due to enlarged glands but is of no value, or actually harmful, in the absence of these symptoms.

Transfusions are of but slight palliative benefit.

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RATE OF SECRETION OF THE PAROTID GLANDS IN NORMAL CHILDREN

A MEASUREMENT OF FUNCTION OF THE AUTONOMIC NERVOUS SYSTEM

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I. HISTORICAL BACKGROUND OF THE PROBLEM

The human salivary glands are among the most complex of all the glands of the body. They are relatively poorly understood, and many controversial issues have sprung up about their mechanisms, secretions and functions. The many inconsistencies in data in the literature are probably due in great part to the differences in technic which were used for the collection and study of their secretions. This is particularly true of the parotid glands. Therefore, the history of knowledge of the secretory reactions of the human parotid glands resolves itself to a large extent into a story of methodologic changes.

From 1832, when Mitscherlich [1] reported his first observations on human parotid secretion, till 1916 there were two methods used for the collection of isolated salivary secretions. These were direct collections from fistulas and collection by the use of cannulation. Six physicians who had patients with fistulas due to accidental cuts or burns did much of the pioneer work in the field. Starting with Mitscherlich, they were Stoney-Butler (1873),[2] Küss (1899),[3] Zebrowski (1904),[4] Smirnov (1921) [5] and Krasnogorski (1926).[6] There have been criticisms leveled at the fistula method on the basis that it involves a structural anomaly in

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1. Mitscherlich, C. G.: Ueber den Speichel des Menschen, Mag. f. d. ges. Heilk. **38**:491, 1832.

2. Stoney-Butler, P.: Effect of Stimuli on the Secretion of the Parotid Gland, J. Anat. & Physiol. **7**:161, 1873.

3. Küss, C.: Notes sur le salive parotienne de l'homme, J. de l'anat. et physiol. **35**:246, 1899.

4. Zebrowski, E.: Zur Frage der sekretorischen Funcktion der Parotis beim Menschen, Arch. f. d. ges. Physiol. **110**:105, 1925.

5. Smirnov, A. I.: The Secretion of the Parotid Gland in Man, Kubanski Nauchno-Med. Vestnik, 1921, nos. 2-4, p. 59.

6. Krasnogorski, N. I.: Ueber die Wirkung der Wärmereize auf die Tätigkeit der Speicheldrüsen bei Kindern, Monatschr. f. Kinderh. **42**:327, 1929.

which the conditions are possibly not applicable to normal functioning. However, even if this technic were reliable in investigations on human beings, subjects are too rare for extensive experimental work.

The first artificial method for collecting parotid secretions was devised in 1860 by Ordenstein,[7] who inserted a small cannula into the mouth of Stenson's duct. Besides being painful, this method proved too unreliable, since the duct expands under such stimulation, permitting the cannula to slip out or the secretions to leak past the cannula. Babkin[8] stated the belief that the cannula itself acts as an artificial stimulant to the gland. When Eckhard, in 1863,[9] and Oehl, in 1864,[10] used this method, they noted definite limitations; but when fairly recent studies,[11] quoted in the literature on the parotid glands, were made with cannulation these limitations were taken into consideration. The inaccuracies of data obtained in the latter experiments were pointed out by Korchin and Winsor.[12]

Studies on the human parotid glands received their greatest impetus with the discovery of a simple and ingenious device, a small suction and collection disk developed by Lashley in 1916.[13] This disk, the diameter of which is about that of a dime and which is about three times as thick, opened the door to a wealth of information on parotid activity in human beings. Without necessitating surgical treatment or subjecting the subjects to pain and discomfort, it made possible the most accurate measurements available of quantitative and qualitative variations in parotid secretion. Ten years later Krasnagorski created a similar device in Russia. His is the chief authoritative work dealing with the parotid secretions in children, its chief interest lying, however, in its treatment of the conditioned and unconditioned reflexes. Winsor's (1929) modification of Lashley's disk was used in compiling the figures on which this paper is based.

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7. Ordenstein, L.: Ueber den Parotidenspeichel des Menschen, Beitr. z. Anat. u. Physiol. **2**:103, 1860.

8. Babkin, B. P.: The Innervation of the Salivary Glands, Tr. Roy. Soc. Canad. (Sect. V. Biol. sc.) **25**:205, 1931.

9. Eckhard, G.: Ueber die Eigenschaften des Sekrets des menschlichen Glandula submaxillaris, Beitr. z. Anat. u. Physiol. **3**:39, 1863.

10. Oehl, E.: La saliva umana studiata colla siringazione dei condotti ghiandolari, Pavia, F. Fusi, 1864.

11. Clark, G. W., and Carter, K. L.: Factors Involved in Reaction Changes of Human Saliva, J. Biol. Chem. **73**:391, 1927.

12. Korchin, B., and Winsor, A. L.: The Relationship of Certain Organic Factors to Individual Differences in Human Parotid Secretory Rate, J. Exper. Psychol. **27**:192, 1940.

13. Lashley, K. S.: The Human Salivary Reflex and Its Use in Psychology, Psychol. Rev. **23**:446, 1916.

Richter and Wada [14] made a contribution to the method when they employed calibrated tubes for measuring the secretory rate. Prior to that time counting drops or determining the volume of saliva collected in test tubes or beakers was used.

There have been several modifications of the method originally used to hold the collecting disk in place in the mouth (Finesinger and Finesinger [15] and Jenness and Hackman [16]). Since the simplest suction method (Winsor and Strongin), described in the following pages, works satisfactorily, the more elaborate technic employed by those investigators has not been used in this study.

II. APPARATUS AND TECHNIC

The complete apparatus for collection and measurement of parotid secretion is called a sialometer. The disk used in these experiments consists of a silver-plated metal disk 14 mm. in diameter, out of which two concentric chambers are cut. The inner, or collecting, chamber is 10 mm. in diameter and 3 mm. deep. The outer chamber, in the form of a circular groove, is 1.5 mm. wide and 5 mm. deep (fig. 1). To provide for greater flexibility in conveying the secretion to the measuring device, rubber tubes of about the same bore are attached to the metal outlets from the chambers of the disks. The rubber tubing attached to the outer, or suction, chamber is about 45 cm. long. The tube which conveys the secretion from the inner chamber of the disk to the measuring device is long enough to extend loosely from the subject to the measuring device, which is situated in front of the experimenter.

The pipets are calibrated to 0.01 cc. Usually a 1 cc. pipet suffices in experiments on unstimulated rates. In order to avoid hydrostatic pressure, the level of the pipet is kept about 6 inches (15 cm.) below the level of the disk in the subject's mouth. It is not necessary to fill the entire collecting system with water or to wait till the saliva fills the tubing leading to the pipet. A 0.05 cc. bead of water in the pipet will be pushed along in the pipet by the column of air in the tubing as the gland secretes.

In use, a suction disk is placed against the inner surface of a cheek so that the central chamber covers the mouth of Stenson's duct. While the experimenter is looking for the opening of the duct he keeps the end of the short piece of rubber tubing in his mouth. As soon as the central chamber of the disk covers the opening of the duct, the experimenter can exhaust the air from the outer chamber of the disk by gently sucking the tube in his mouth. He then clamps off the tubing. The disk clings tightly to the check, and the secretion is free to flow into the central chamber and to push the column of water through the rubber tubes and recording device. It was found that elaborate suction pumps, bulbs and other methods of applying the suction were not as satisfactory as the simple method just described. Care is taken to avoid applying too much suction. (The suction is released at the end of the experimental period before the disks are removed.) The disks and

14. Richter, C. P., and Wada, T.: Method of Measuring Salivary Secretions in Human Beings, J. Lab. & Clin. Med. **9**:271, 1922.

15. Finesinger, J. E., and Finesinger, G. L.: Modification of Krasnogorski Method for Stimulating and Measuring Secretion from Parotid Glands in Human Beings, J. Lab. & Clin. Med. **22**:267, 1937.

16. Jenness, A., and Hackman, R. C.: Salivary Secretion During Hypnosis, J. Exper. Psychol. **22**:58, 1938.

rubber tubes and the hands of the experimenter are of course always carefully cleaned and sterilized before each experiment.

In order to avoid the factors of hunger or satiation—both of which affect the secretory activity of the glands—all crucial experiments are performed about one

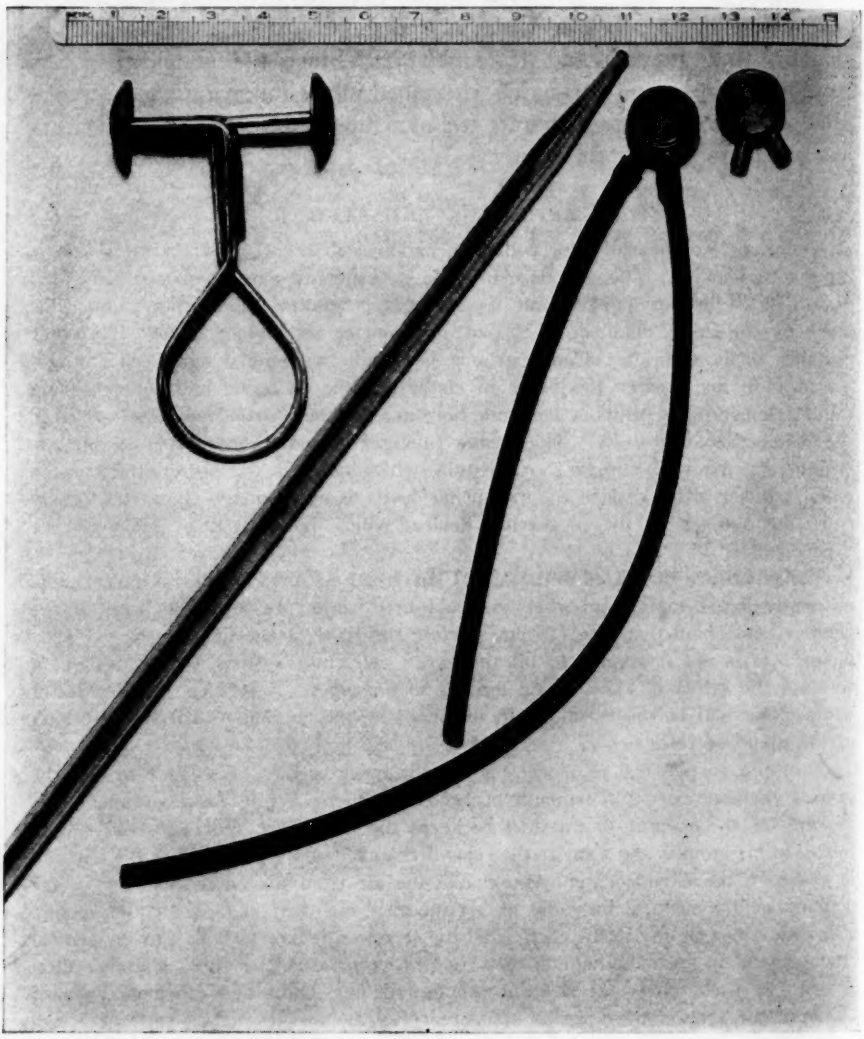

Fig. 1.—Apparatus for collection of saliva from the parotid glands.

and one-half to two hours after mealtimes. A consideration of the nature of the activation of the glands prior to an experiment or any part of an experiment is always imperative. In experiments which involve several changes in secretory activity time is allowed for the activity to return to normal before the next portion of the experiment is undertaken.

Attempts are made to put the subject at his ease and to accustom him to the laboratory situation. The child knows he will have a reward at the end of the "test." He is given one of the disks to play with, and he is encouraged to put it into his mouth to prove to himself that it is not painful. The apparatus is described to the subject, and its method of operation demonstrated. The subject is told that the disks should cause no discomfort at all. However, if too much suction is applied or if the disks are not placed directly over the openings of the ducts, the subject may experience some discomfort, in which event the disks are immediately removed. The subject is told before the onset of the experiment that if he experiences any pain or discomfort he shall inform the experimenter and the experiment will be terminated.

When applied correctly the collecting device itself does not affect the flow of secretion or seriously interfere with the oral movements of the subject. Experiments which had been performed on the effects of mechanical stimulation of the oral mucosa indicated that the effect of the presence of the disks on the secretory activity is negligible. The subject quickly becomes adapted to the presence of the disks and after a few minutes is usually quite comfortable. Even with disks on both parotid ducts the subject is able to converse and eat and drink in a normal fashion.

The subject is seated in front of a small table and is instructed to assume a comfortable posture. For records of a control, that is the secretory reaction in a condition without marked external stimulation, the subject is instructed to avoid excitatory movements of the tongue or throat, except as directed. In order that the accumulated secretions from the other salivary glands will not interfere with the subject's comfort, he is permitted to swallow at a given signal at the end of every five minute period when the control secretions are obtained. In view of the fact that swallowing increases the rate of flow, the secretion during the minute in which swallowing takes place is not included in the record of the control secretion. For the needs of the experiments reported in this paper the rate of flow was recorded every minute, accurately timed by means of a stopwatch.

To avoid the factor of dehydration (this is discussed more fully in part IV), if there is a suspicion of its presence clinically or in the history of intake and excretion of fluid, a McClure-Aldrich test is done (measuring the rate of absorption of 0.1 cc. of physiologic solution of sodium chloride injected intradermally).

The test period lasts twenty to thirty minutes (four to six periods of five minutes). No test is considered valid if it does not include three periods of five minutes.

A disk is applied to both the right and the left parotid duct whenever possible. The advantages of using both glands are many. It affords a check on the apparatus. A leak or other disturbance may be indicated if on stimulation only one of the glands responds normally. In addition, most persons have been found to have a certain amount of glandular dominance in parotid activity. Therefore, collection of secretions from both glands gives a truer picture of the average secretory activity. Collecting secretions from both sides also makes possible studies on organic neurologic problems which may eventually turn out to have some

implications in the localization of lesions of the brain of various types. These could not be investigated by the earlier method of using only one gland.

The isolation of the secretions from the other large salivary glands has not been satisfactorily accomplished thus far. Krasnagorski [17] and Gore (1937) have advocated the use of special suction disks which have not as yet been entirely adequate in actual use. Winsor and Korchin, after isolating the parotid secretions with disks as previously described, aspirated or had absorbed on tarred absorbent material (after Poth [18]) the secretions from the other glands, which could then be studied separately.

This investigation is concerned only with the unstimulated, inactivated or "resting" rate of parotid secretion. Therefore, my only contact with the large and important field of salivary stimulants has been with the use of lemon juice given at the onset of an experiment in those rare tests on children in whom there is no flow shortly after the disks are in place. This serves as a check on the correct application of the disks. At least five minutes must be allowed for the rate to become normal after a few drops of lemon juice is given. Some experiments are being carried on with olfactory stimuli which can be used to produce homolateral parotid activity (Ellsberg, Spotnitz and Strongin [19]). This is not in agreement with Lashley's [13] conclusion that "there is no direct reflex to olfactory . . . stimulation."

III. INNERVATION OF THE PAROTID GLANDS

Since this study has in its final analysis many implications in cortico-glandular relationships, it is felt that an outline of the probable neural connections of the parotid glands is worth while, especially in regard to their relations to the mechanisms of the autonomic nervous system.

The parotid glands are supplied by nerves derived from the parasympathetic and sympathetic nervous systems. Faradic stimulation of nerve cells at two definite points on the floor of the medulla oblongata on one side produces secretion from the ipsilateral salivary glands. Anatomic investigation by Kohnstamm,[20] Yagita and Hayama,[21] and the

17. Krasnogorski, N. I.: Bedingte und unbedingte Reflexe im Kindesalter und ihre Bedeutung für die Klinik, Ergebn. d. inn. Med. u. Kinderh. **39**:613, 1931.

18. Poth, E. J.: Simplified Technic for Quantitative Collection of Saliva from Man, Proc. Soc. Exper. Biol. & Med. **30**:977, 1933.

19. Elsberg, C. A.; Spotnitz, H., and Strongin, E. I.: Effect of Stimulation by Odorous Substances upon Amount of Secretion of Parotid Glands, J. Exper. Psychol. **27**:58, 1940.

20. Kohnstamm, O.: Der Nucleus salivatarius Chordae tympani, Neurol. Centralbl. **21**:848, 1902.

21. Yagita, K.: Untersuchungen über das Speichelzentrum, Anat. Anz. **35**:70. 1910.

histophysiologic investigations of Miller,[22] established that this group of nerve cells, which Kohnstamm called the nucleus salivatorius, runs from the sensory nucleus of the seventh nerve down to the anterior end of the nucleus ambiguus. The more posterior portion of this group of cells, the so-called nucleus salivatorius inferior (or posterior), sends secretory (parasympathetic) fibers to the homolateral parotid gland. There is no sharp division between the salivary nerve fibers carried in the seventh and in the ninth cranial nerve, and Reichert and Poth [23] have stated the opinion that the parotid glands in human beings receive their secretory fibers from both of these cranial nerves. The preganglionic fibers from the ninth nerve to the parotid gland traverse the tympanic cavity as Jacobsen's nerve and reach the otic ganglion with the small superficial petrosal nerve. Postganglionic fibers arise from the ganglion and reach the gland through the auriculotemporal nerve. The sympathetic nerve fibers of the parotid gland are derived from the cervical portion of the sympathetic system through the superior cervical ganglion and reach the gland as postganglionic fibers along the arteries to the parotid gland.

In the diencephalon, particularly in the hypothalamic centers which regulate control of visceral functions, there are groups of cells which are related to salivary activity. Müller [24] stated that stimulation of the subthalamic area results in secretion of saliva and tears. Papez [25] expressed the opinion that salivary reactions are mediated through the dorsomedial and ventromedial nuclei of the hypothalamus (small-celled nuclei). Stimulation of these areas reduces heart rate and increases salivation, tonus of the urinary bladder and intragastric pressure. These effects are stopped by atropine. The lateral and posterior hypothalamic area, which contains the larger motor-like cells, is said on stimulation to produce marked inhibition of gastrointestinal peristalsis, decreased salivation, increased blood pressure and reduced intragastric pressure, metabolic activity and heat production. Lesions in or destruction of these areas give results opposite to stimulation. From the foregoing observations it may be assumed that there is not only parasympathetic control exerted by certain subthalamic areas but sympathetic control as well. Sixty years ago Lépine and Bochefontaine [26] discovered that stimulation with an induction current of the cerebral cortex behind and below the sulcus

22. Miller, F. R.: On the Reactions of the Salivary Centers, Quart. J. Exper. Physiol. **6**:57, 1913.

23. Reichert, F. L., and Poth, E. J.: Pathways for the Secretory Fibers of the Salivary Glands in Man, Proc. Soc. Exper. Biol. & Med. **30**:973, 1933.

24. Müller, L. R.: Lebensnerven und Lebenstriebe, ed. 3, Berlin, Julius Springer, 1931, p. 180.

25. Papez, J. W.: Cerebral Mechanisms, J. Nerv. & Ment. Dis. **89**:145, 1939.

26. Lépine, R., and Bochefontaine, L.: L'influence de l'excitation du cerveau sur la sécrétion salivaire, Gaz. méd. de Paris **46**:332, 1875.

cruciatus in a dog produces secretion of saliva from the parotid glands, and this observation has been confirmed by many later investigations (Babkin 1938). Fulton, Kennard and Watts [27] gave Vogt and Brodman's area 6 aβ as a center which on stimulation produces salivation. In general, it is stated that the center for salivary reactions is in the premotor area near the area representing the face. Papez [25] stated the belief that this evidence gives only a fraction of the total picture and that the more important regions for autonomic representation in the cerebral cortex are to be found elsewhere, probably in the region of the gyrus cinguli and the hippocampus. The pyramidal and extrapyramidal fibers have been suggested as the connecting links with the lower centers (Spiegel and Hunsicker, 1936). However, these areas of the cortex are not to be regarded as ordinary "centers" for salivary secretion, for Tichomirov [28] revealed that the conditioned salivary reflexes did not disappear after extirpation of these areas in both hemispheres in a dog. This emphasizes Goldstein's [29] hypothesis that the "functional" center is not identical with the anatomic and that only "castastrophic" situations can lead to functional paralysis of an organ.

The afferent nerves of the parotid glands are carried in the glossopharyngeal, lingual, buccinator and palatine nerves and in the pharyngeal branch of the vagus.

Stimulation of the parasympathetic nerves leading to the parotid glands produces both a secretory and a vasodilator effect on these glands. The effects transmitted through the sympathetic nerves are of three types: "trophic," "motor" and "vasoconstrictor." Heidenhain [30] introduced the concept of the "trophic" effect of a glandular nerve, implying the conversion into soluble form and subsequent discharge of colloidal organic material stored in the secretory cells. This function of the glandular nerves is entirely distinct from their secretory function, by means of which the passage of water and salts from the blood through the secretory cells is regulated. Heidenhain [31] held that the trophic fibers are supplied to glands by the sympathetic nerves, while the secretory fibers originate chiefly from the parasympathetic system. Confirmation of this theory is found in the report that stimulation of the sympathetic fibers to a parotid gland (provided the parasympathetic

27. Fulton, J. F.; Kennard, M. A., and Watts, J. W.: Autonomic Representation in the Cerebral Cortex, Am. J. Physiol. **109**:37, 1934.

28. Tichomirov, N. P.: Thesis, St. Petersburg, 1906.

29. Goldstein, K.: The Organism, New York, American Book Company, 1939.

30. Heidenhain, R.: Ueber sekretorische und trophische Drüsennerven, Arch. f. d. ges. Physiol. **17**:1, 1878.

31. Heidenhain, R.: Beiträge zur Lehre von der Speichelabsonderung, Studien, des physiologischen Institutes zu Breslau, Leipzig, Breitkopf & Hörtel, 1868, pt. 4, p. 1.

fibers have not been stimulated shortly before and the tympanic nerve has been cut to prevent a reflex effect) produces no perceptible flow from the gland (Howell [32] and Best and Taylor [33]). It does produce, however, a striking change in the subsequent type of saliva secreted by the gland, the organic matter being often tenfold that obtained by stimulation of the parasympathetic fibers alone.

Some investigators in the field do not agree on this point (Babkin [34] and Baxter [35]), but they generalize about the secretory innervation of all the salivary glands and have not limited their discussions to the parotid glands. This is evident from Babkin's argument, in which he postulated that the parasympathetic nerve fibers innervate the mucous cells of the salivary glands while the sympathetic fibers produce changes in the serous cells. This obviously applies only to the mixed glands, because the parotid glands are, on the basis of the best authorities, completely serous glands. In addition, he based some of his statements on evidence accumulated by Rawlinson [36] in studies on cats, whose salivary reactions are known to be different from those of man. Various authors have suggested that the three pairs of large salivary glands respond normally to different stimuli, and Pavlov [37] supported this view.

The "motor" effect of the sympathetic nerves on a parotid gland consists of a contraction of the gland under sympathetic stimulation. This has been confirmed by Anrep and Khan.[38] Subsequent investigations showed that the contraction of the gland is not effected by muscular tissue but is probably brought about by the special contractile myoepithelial cells (Babkin and McKay [39]) lying between the membrana propria and the basal part of the cells.

32. Howell, W. H.: A Textbook of Physiology, ed. 14, Philadelphia, W. B. Saunders Company, 1940.

33. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, Baltimore, William Wood & Company, 1937.

34. Babkin, B. P.: (*a*) The Physiology of the Salivary Glands, Dental Science and Dental Arts, edited by Gordon, Philadelphia, Lea & Febiger, 1928, p. 219; (*b*) footnote 8.

35. Baxter, H.: The Influence of Section of the Cervical Sympathetic Nerve and Extirpation of the Superior Cervical Ganglion on the Composition of the Parotid Saliva in the Dog, Am. J. Physiol. **97**:668, 1931.

36. Rawlinson, H. E.: Cytological Changes After Autonomic and Adrenalin Stimulation of the Cat's Submaxillary Gland, Anat. Rec. **57**:289, 1933.

37. Pavlov, I. P.: The Work of the Digestive Glands, translated by W. H. Thompson, ed. 2, London, C. Griffin & Co., 1910, p. 32.

38. Anrep, G. V., and Khan, H. N.: The Metabolism of the Salivary Glands: V. The Process of Reconstruction of the Submaxillary Gland, J. Physiol. **58**:302, 1924.

39. Babkin, B. P., and MacKay, M. E.: Concerning the Motor Mechanism of the Salivary Glands, Am. J. Physiol. **91**:370, 1930.

The hormonal control of parotid activity is also a controversial subject. Cannon and his associates [40] demonstrated that stimulation of sympathetic fibers conveying impulses to smooth muscles of the vessels of the legs or of the splanchnic region produces sympathomimetic effects in many distant organs, including the salivary glands, by the liberation in the body of sympathin. This same substance is liberated by stimulation of the sympathetic fibers innervating the salivary glands (Cattel, Wolff and Clark [41]), and there is little doubt that this adrenergic agent transmits the impulses from the sympathetic nerve fibers to the gland cells. On the other hand, Sacks and Kim [42] stated that the secretory activity of the salivary glands is regulated exclusively by the nerves and that there is no specific hormonal mechanism for salivary secretion. The preponderance of evidence points to the functional interdependence of the vegetative nervous system and the endocrine glands, but as yet this relationship obviously is unclarified. Hoskins [43] remarked about this: "In the meantime it is not wise to be misled into a feeling of false security by premature schemata purporting to set forth these relationships so that he who runs may read."

To summarize from the preceding discussion the points most important in evaluating and explaining the results of this study, it may be said that the preponderance of evidence shows that the secretory activity of the parotid glands is controlled primarily by the parasympathetic nervous system and that the sympathetic system has no effect on rate. However, before being willing to say to any extent that what is measured with the rate of parotid secretion is primarily parasympathetic function, I should have to convince myself that the sympathetic innervation had no primary effect on this rate. In an attempt to show this small doses of epinephrine hydrochloride (0.1 cc.) of a 1 : 1,000 solution were given hypodermically to 3 children (ages 5, 8 and 9 years) after their characteristic rates had been established. This was enough to raise the blood pressure 30 to 50 mm. of mercury, to increase the pulse rate 50 to 70 beats and to produce moderate evidence of vasoconstriction (pallor, etc.). However, no great change in parotid secretory

40. Cannon, W. B., and Bacq, Z. M.: Studies on the Conditions of Activity in Endocrine Organs: XXVI. A Hormone Produced by Sympathetic Action of Smooth Muscle, Am. J. Physiol. **96**:392, 1931. Cannon, W. B., and Rosenblueth, A.: Autonomic Neuro-Effector Systems, New York, The Macmillan Company, 1937. Studies on Conditions of Activity in Endocrine Organs: XXIX. Sympathin E and Sympathin I, Am. J. Physiol. **104**:557, 1933. Cannon, W. B.: Chemical Mediators of Autonomic Nerve Impulses, Science **78**:43, 1933.

41. Cattel, M.; Wolff, H. G., and Clark, D.: The Liberation of Adrenergic and Cholinergic Substances in the Submaxillary Gland, Am. J. Physiol. **109**:375, 1934.

42. Sacks, J., and Kim, M. S.: On the Non-Existence of a Hormone for Salivary Secretion, Proc. Soc. Exper. Biol. & Med. **27**:193, 1929.

43. Hoskins, R. G., and Lee, M. O.: The Internal Secretions and the Autonomic Nervous System, A. Research Nerv. & Ment. Dis., Proc. (1928) **9**:361, 1930.

rate was noted. In 2 instances it went up slightly for two minutes ("motor" effect?); in the third, it went down after a slight rise. The rates in all subjects remained within the same range they had been in before administration of the drug. However, when a larger dose of epinephrine hydrochloride solution was given fifteen minutes later, a dose large enough to produce symptoms of alarm and mild shock in the subjects (0.5 cc.), the rate definitely went down. (For a discussion of the effect see the section on pharmacologic reactions in part IV.)

Further corroboration of the thesis that it is primarily the effect of the parasympathetic nerve on the glands which is measured by the use of the parotid secretory rate was found clinically during a study of 2 children who were hospitalized at Babies Hospital for obvious sympathetic imbalances. These children had fluctuating high blood pressures, unstable pulse rates, marked vasomotor changes in the skin, dermographia, etc. Their parotid secretory rates in each instance were definitely within the normal range and did not vary with the changes in the other signs and symptoms as might be expected if this rate were a sympathetically determined function.

IV. PHYSIOLOGIC AND PSYCHOLOGIC ASPECTS OF UNSTIMULATED, OR RESTING, PAROTID SECRETION

The physiologic and psychologic factors affecting the rate of secretion of a resting parotid gland are important in this problem because they must all be taken into consideration in actual performance of the tests and evaluation of the results. In general, it may be said that the end results of most conditions affecting the rate may be related to the protective, moistening, cleansing and digestive functions of the parotid secretions. Before these factors are examined, however, it would not be amiss to review what is known concerning this rate of secretion while the glands are at rest.

There is considerable difference of opinion in the literature concerning the occurrence of a continuous secretion of saliva in human beings during rest. The results reported before Lashley's disk came into use differed in both fact and theory. Since then a great deal has been learned about the existence of this rate and the factors which control it. Since the observations before 1916 were not evaluated in terms of these factors, it is best to leave them out of this discussion with only enough mention of them to show the previous disagreement. For instance, Mitscherlich,[1] Ordenstein,[7] Stoney-Butler,[2] Küss [3] and Krasnogorski [6] reported unactivated parotid secretions in their subjects with fistulas or in their cannulated subjects. Zebrowski [4] and Brunacci [44] took the opposite stand on the question.

44. Brunacci, B.: Sulla funzione secretoria della parotida nell'uomo; nota prima; influenza della qualità dello stimolo sulle proprietà fisicochimiche della saliva parotidea, Arch. di fisiol. **8**:421, 1910.

Following Lashley, Morris and Jersey,[45] Allen,[46] Birukov,[47] Krasnogorski,[17] Winsor[48] and Strongin,[49] all noted an unstimulated resting secretion. Babkin in 1914 argued against the presence of such a secretion, but in his later reviews on the subject [50] he reversed his stand somewhat, leaving the question open. However, he cited evidence against such a rate from experiments on animals, which since have been repeated in the light of newer knowledge. For instance, while Mangold [51] and Pavlov [52] (1927) failed to find spontaneous, continuous secretion in dogs and observed it only in ruminant animals, Gooreev [53] and Liddell (1938) have found a small amount of such secretion in dogs. Lashley [54] stated that the resting secretion "may be reflex in nature, since there is probably a constant stimulation of the mucosa of the digestive tract." Winsor [55] interpreted his findings on resting secretions to indicate a glandular tonicity analogous to that of muscular tonus.

For convenience the chief conditions affecting the parotid activity may be grouped into five categories: local effects, general conditions, factors related to the nervous system, gastrointestinal conditions and pharmacologic reactions. Some of the factors could be fitted into more than one group, and often they were arbitrarily placed in one or another category for convenience in presentation.

Local Effects.—1. The question of whether or not the disks themselves might activate the glands was considered by Lashley [54] and later

45. Morris, J. L., and Jersey, V.: Chemical Constituents of Saliva as Indices of Glandular Activity, J. Biol. Chem. **56**:31, 1923.

46. Allen, F.: The Secretory Activity of the Parotid Gland, Quart. J. Exper. Physiol. **19**:336, 1929.

47. Birukov, D. A.: Unconditioned Salivary Reflexes in Man, Rostov-on-Don, U. S. S. R., State Publishing House, 1935.

48. Winsor, A. L.: Conditions Affecting Human Parotid Secretion, J. Exper. Psychol. **11**:355, 1928.

49. Strongin, E. I., and Hinsie, L. E.: Parotid Secretory Rate in Schizophrenic Patients, J. Nerv. & Ment. Dis. **87**:715, 1938.

50. Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, ed. 2, Berlin, Julius Springer, 1928; footnote 34 *a*.

51. Mangold, E.: Handbuch der Ernährung und des Stoffwechsels der landwirtschaftlichen Nutztiere als Grundlagen der Fütterungslehre, Berlin, Julius Springer, 1929, vol. 2, p. 113.

52. Pavlov, I. P.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, translated and edited by G. V. Anrep, New York, Oxford University Press, 1927.

53. Gooreev, T. T.: The Periodic Activity of the Salivary Glands, Conditioned Reflexes, Collected Papers of the Psychoneurological Institute of the Ukraine Kharkov, 1932, p. 187.

54. Lashley, K. S.: Reflex Secretion of the Human Parotid Gland, J. Exper. Psychol. **1**:461, 1916.

55. Winsor, A. L.: Observations on the Nature and Mechanism of Secretory Inhibition, Psychol. Rev. **37**:399, 1930.

by Winsor.[48] They demonstrated that the activating influence of the disks themselves is negligible.

2. Muscular exercise expressed in terms of local changes about the oral cavity, i. e. swallowing and similar activities, such as movements of the mouth, sucking on the disks, yawning and belching, causes a slight rise in rate. On the other hand, with intense more generalized muscular exercise a slight increase in rate is shortly followed by a moderate drop (Nekrassov and Khranilova [56]).

3. Some of the Russian investigators have described a so-called "water reflex"; i. e., water placed into the mouth causes a flow of parotid saliva (Birukov [47]). However, this has been found to be more of a local temperature effect. With temperatures above and below that of the body there is an increase of flow. Water at 37.5 C. in the mouth has no observable effect on the secretory rate (Brunacci [44]).

4. Local irritations, such as painful dental conditions or oral lesions, cause an increase in rate. This is most likely an expression of the protective function of saliva in the mouth.

5. The fatigue of the parotid glands themselves or the exhaustion of the secretory supply was often considered to be a possible disturbing factor in experimental work. However, Lashley [13] recorded little change in secretions when the glands were activated for ten minutes. Winsor [57] reported no marked diminution after fifty minutes of chewing. Heidenhain [30] (with weak induction shocks) obtained a secretory activity which kept up for "hours." Apparently the parotid glands are relatively indefatigable.

6. The state of the glands at the time of the test is important in the test, not from the point of view of previous activity, which as has just been shown has little effect, but in regard to inactivity. Winsor [57] found that "within certain limits the longer the rest periods preceding excitation, the more rapid the subsequent rate of secretion." This "reservoir" effect may account for the increased secretory flow on awakening from sleep.

General Conditions.—1. Careful studies made by Korchin [12] on the effect of weight, height, pulse rate and blood pressure on the rate of parotid secretion showed no correlation between them. Certainly the investigation of somatic components has thrown no light on the question of the wide range of individual differences. Apropos of the studies on blood pressure, it may be noted in passing that the pressure of

56. Nekrassov, P. A., and Khranilova, N. V.: The Influence of Physical Work on the Unconditioned Salivary Reflex in Man, Arkh. biol. Nauk **35**:593, 1934.

57. Winsor, A. L.: The Effect of Mental Effort on Parotid Secretion, Am. J. Psychol. **43**:434, 1931.

the parotid secretion is consistently higher than blood pressure and is apparently not related to it.

2. Dehydration is of course a pronounced factor in reduction of rate, since the salivary output is to a great extent dependent on the water balance of the organism. Gregersen and his co-workers [58] emphasized the influence of thirst on the rate of salivary secretion, and Winsor [59] reported the cutting down of parotid secretions by 50 per cent in one hour when dehydrating agents were used. The normal secretory rate was quickly restored when liquid was ingested. Precautions may be taken in this regard by using the McClure-Aldrich technic of evaluating roughly the water balance of the body by a cutaneous test (part II).

3. Infectious diseases, especially rabies and smallpox, often cause an increase more marked than that accounted for by higher temperatures. In parotitis the secretions are lowered (Krasnogorski [17]).

4. Position of the body is important in the test. Standing diminishes the rate of secretion, and it is possibly this factor which explains Pavlov's reports [60] that no "inactivated" secretions were found in the dogs (which were standing when tested) used in his experiments. Lying down will similarly cause a reduction in secretion. Sitting comfortably is the position of choice for the patient.

Factors Related to the Nervous System.—1. Sleep has a definite inhibitory effect on rate of parotid secretion. This effect is roughly proportional to the depth of sleep. The investigator can usually tell when a subject has fallen asleep in the middle of an experiment because of the change in rate. In hypnosis too (Jenness and Hackman [16]) there is a similar reduction in rate, varying with the depth of hypnosis.

In coma of the hypoglycemic type (during treatment with insulin) it was found that there is a sharp rise in rate with the onset of the stuporous state (Strongin, Hinsie and Harris, 1938). However, while the patients slept, as they often do during the earlier stages of an insulin treatment, the rate showed a drop. There is, therefore, a differential point, detected by the use of this apparatus, between coma and sleep, and certainly the technic should be valuable in future research on sleep itself.

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58. Gregersen, M. I.: Conditions Affecting the Daily Water Intake of Dogs as Registered Continuously by a Potometer, Am. J. Physiol. **102**:344, 1932. Gregersen, M. I., and Bullock, L. T.: Observations on Thirst in Man in Relation to Changes in Salivary Flow and Plasma Volume, ibid. **105**:39, 1933. Gregersen, M. I., and Cannon, W. B.: The Effect of Extirpation of the Salivary Glands on the Water Intake of Dogs While Panting, ibid. **102**:336, 1932.

59. Winsor, A. L.: The Effect of Dehydration on Parotid Secretion, Am. J. Psychol. **42**:602, 1930.

60. Pavlov, I. P.: Lectures on Conditioned Reflexes, translated by W. H. Gantt, New York, International Publishers, 1928; footnote 52.

Closely related to this question is that of anesthesia. While no studies have been made on human beings, Robbins [61] reported of dogs: "All of the anaesthetics cause a cessation of salivary secretion during anaesthesia by depressing the secretory center." He also found that ether and chloroform cause an increased secretion in dogs during induction.

2. Emotional factors have long been known to have definite effects on the body secretions. As far as the secretory rate of the parotid glands is concerned, it has been determined that minor emotional reactions cause a slight increase in secretion while more intense emotional experiences, such as excitement, fear, etc., after causing a transitory rise in output produce an inhibition (Wittkower and Pilz; Korchin and Winsor [12]). Farr [62] pointed out the same phenomenon in gastric secretion. Disgust, embarrassment, pain and erotic emotions have also been shown to have a depressing effect on the rate of parotid secretion, while pleasurable sensations may increase the rate slightly. Although Lashley [13] concluded that "there is no direct reflex to olfactory, ordinary visual, auditory or tactile stimulation," subsequent investigators have tended to disagree with him.[19]

3. The development of conditional salivary reflexes in human beings is another controversial area. Richter and Wada [14] have denied that such conditioning is possible, while Lashley,[54] Smirnov [5] and Krasnogorski [17] among others have said that it is possible. Winsor and Bayne [63] suggested that the conditioned reflexes set up in human beings depend on a multiplicity of intrinsic and extrinsic factors. For example, the reflexes set up with food seem to depend largely on the state of hunger of the subject. Certainly the conditioning process, even in children, is a much more complicated one than in dogs, and the reflexes, when and if established, are not stable. Their effect on secretion in any case is transitory, lasting at the most a few minutes. Therefore, if any such process was unwittingly set up by the test procedure, perhaps by some such factor as the subject's knowledge that he was to get a lollypop after each test, its effect would be only short lived and would not be reflected to any great extent in the results of the tests, which extended over a period averaging twenty to twenty-five minutes.

4. It has been determined that there is usually in human beings a dominance of one parotid gland which is consistent for any given person.

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61. Robbins, B. H.: Effect of Various Anesthetics on Salivary Secretion, J. Pharmacol. & Exper. Therap. **54**:426, 1935.

62. Farr, C. B.: Effect of Emotion on Gastric Secretion, Baltimore, Wilkins & Wilkins Company, 1931, p. 217.

63. Winsor, A. L., and Bayne, T. L.: Unconditioned Salivary Responses in Man, Am. J. Psychol. **41**:271, 1929.

Korchin [12] has found that males are predominantly left glanded and females right glanded. This correlates well with Pende's [64] observation that males are usually left glanded over their whole bodies (the left testicle larger than the right), while females are predominantly right glanded (right breast and right lobe of thyroid larger, etc.). This has no correlation with handedness, footedness or eyedness, however. In my studies on children I have not found any consistent sex-determined glandedness. It has been suggested as possible that when sex hormones are changed from their even balance of prepubescence to a male or female preponderance after puberty, glandedness could also conceivably change. This is a highly speculative question and is of only academic interest now.

5. Mental work, concentration on a task or a problem, causes in most subjects a decrease in rate. I have been able to confirm Birukov's [47] and Winsor's [57] observations on this point, except that on rare occasions in my experiments a child working on a problem during a test period showed no change or even a slight rise in secretion. Possibly this is caused by concomitant movements of the mouth and tongue, as suggested by Lashley. It is interesting in this connection to note that when a series of 10 mongolian idiots under 12 years of age were given a picture game to work on during part of the test the rate consistently increased. I am unable to explain this paradoxic reaction.

6. In schizophrenia and depressions of the manic-depressive type in adults, rates of parotid secretion show decided changes (Strongin and Hinsie [49]). While persons with early schizophrenia had little change in rate from normal, the more deteriorated subjects showed an acceleration in rate. This increase was proportional to the degree of regression. This will be considered later in the light of some of my data. In manic-depressive depression there is a complete or almost complete inhibition of rate, which is so consistent that it has been considered as an aid in differential diagnosis between this type of depression and others.

7. Lesions of the central nervous system should, if my outline of the neuroanatomy of the parotid gland is valid, produce changes in rate. It has been found by Lashley,[65] by Elsberg and Spotnitz (unpublished data) and by me in my own investigations that this is true. Lashley's observations were made on patients with fully developed hemiparesis or hemiplegia. He concluded: "The greater secretion in every case appeared on the side showing the more thorough involvement in the paralysis." Elsberg and Spotnitz found unilateral changes in rate with

64. Pende, N.: Constitutional Inadequacies, Philadelphia, Lea & Febiger, 1928.

65. Lashley, K. S.: Changes in the Amount of Salivary Secretion Associated with Cerebral Lesions, Am. J. Physiol. **43**:62, 1917.

certain types of tumors of the brain in adults. These and Lashley's observations are true for children.

Gastrointestinal Conditions.—Gastrointestinal conditions have decided effects on the secretory rate of the parotid glands at rest. To summarize the considerable literature on this point, it may be said that hunger and fasting inhibit the parotid secretion while satiation causes its enhancement. Therefore, it is important to perform tests about two hours after mealtime, to avoid both the postprandial rise and the preprandial decline.

Hisada [66] in 1930 showed that distention of the stomach brings about an increase in rate of parotid secretion (possibly a reflex response via the vagus). He also found that subnormal gastric temperature depresses the rate while supernormal temperatures result in an increased flow.

The only observations on the effects of diet on secretory rate in human beings were those of Ordenstein,[7] who found no correlation between type of food ingested and rate of flow.

As would be expected, the parotid glands respond most readily to gustatory stimuli, and it is on this fact that most of the conditioning experiments were based in the past.

Pharmacologic Reactions.—The usual reactions to drugs which affect the parasympathetic and sympathetic nerves hold true for the parotid glands. Often paradoxic effects of the use of these drugs are found in children, which has discouraged me from extended pharmacologic experiments. This reversal of effect has been explained in many ways. Langley [67] thought of it before the experiments of Fröhlich and Loewi [68] as due to the action of a sympathetic drug on parasympathetic end apparatus or vice versa. He also spoke of the reversal as showing that the action is determined by the condition of the tissue and is not an expression of normal neural action. Epstein [69] theorized that a balanced central nervous system reacts to a stimulus in a constant way. In other words, the condition of the central nervous system may determine the result of the reaction. Another explanation depends on Cannon's homeostatic and Jelliffe's homeokinetic concepts, according to which the different reactions can be explained by the shifting of calcium and potassium ions in the cells, by the general condition of the receptive substance, by the organs of internal secretion and by conscious and

66. Hisada, K.: Ueber die reflektorische Speichelsekretion durch Magenaufblähung, Arch. f. d. ges. Physiol. **224**:249, 1930.

67. Langley, J. N.: The Salivary Glands, in Schefer: Text-Book of Physiology, London, Y. J. Pentland, 1898, vol. 1, p. 475.

68. Fröhlich, A., and Loewi, O.: Ueber vasokonstriktorische Fasern in der Chorda tympani, Zentralbl. f. Physiol. **20**:229, 1906; Arch. f. exper. Path. u. Pharmakol. **59**:64, 1908.

69. Epstein, A.: The Reflexes of the Vegetative Nervous System, Leningrad, U. S. S. R., State Publishing House, 1925.

unconscious psychic factors. The method of administration and the dosage do not often seem to be essential factors. The most important factor which Sachs [70] has been able to arrive at in explaining these seemingly paradoxic reactions to a drug is the previous state of excitability and tonus of the sympathetic or parasympathetic system. He stated that "when the excitability reaches its maximum, a further stimulation of the same nerve will accordingly lead to a paradoxical reaction." For example, a single injection of a pilocarpine salt increases the secretory rate of a child's parotid gland, while a second injection fifteen minutes later, instead of increasing the rate further, will cause the enhanced rate to decrease somewhat.

It is important to know that in the evaluation of the foregoing physiologic and psychologic factors on the rate of parotid secretion in children it has been noticed that while any one factor may increase or decrease the rate the degree of change is seldom sufficient to change a child's reaction from the range that is characteristic of his age group. (This is discussed more fully later in this study.)

V. RATE OF PAROTID SECRETION IN NORMAL CHILDREN

The establishment of normal standards for the secretory rate of the parotid glands in children, essential for the evaluation of the findings in abnormal states, was undertaken with rigid standards for normality of the subjects. The children included in this group were known to be normal physically, to have no known personality deviations and to be making good social and school adjustments. When possible, children were selected who had been subjected to a period of stress and had reacted without disturbance to the trying situation. Such children were made available through one of the large foundling hospitals, where detailed records are kept from early childhood for most children. Many of the subjects were picked from the Normal Child Development Study at the Babies Hospital, where they had been followed regularly, often daily, with many technics since they were 10 days of age. These subjects were particularly valuable in the younger age groups (under 4 years), in which the cooperation and other attributes needed in this procedure would not ordinarily be present in youngsters not used to having proceedings of all types carried out on them. Although it was later apparent that there is no correlation between the intelligence quotient and the parotid secretory rate, all the children used were of average intelligence.

A total of 51 children were selected thus, ranging in age from 3 to 14 years. Nine age groups were established, the subjects from 11 to 14 years being grouped as one for convenience and because of similarity

70. Sachs, W.: The Vegetative Nervous System, London, Cassell & Co., Ltd., 1936.

in rate. Until proper disks are devised, the study of the secretory rate of the unstimulated, or resting, parotid gland in children under 3 years of age will be unsatisfactory for mechanical reasons. In the younger age groups at the start age in months was used, but the variations in rate from child to child in any age group were too gross for such fine differentiation. The results will be found in the table.

Figure 2 graphically shows the relationship of parotid salivary rate to age. The extremely high rates are apparently normally confined to the younger age groups (3 to 5 years). From 5 to 7 years of age the rates are much lower, being one-half to one-fourth that of the earlier age ranges. From 7 to 14 years there is a gradual, slightly uneven drop to levels which approach in early puberty those of normal adults (0.02 to 0.12 cc. per five minutes; average, 0.07 cc. per five minutes). These figures do not confirm Lashley's statement that the rates of children are somewhat lower than those of adults.

Secretory Rate of the Parotid Gland of Normal Children

Age, Years	Number of Children	Mean Rate in 0.01 Cc. per Five Minutes	Range
3-4	5	74.2	59-98
4-5	6	52.6	35-70
5-6	5	24.1	19-30
6-7	7	15.8	6-26
7-8	6	12.8	4-22
8-9	8	15.7	3-22
9-10	4	8.9	5-14
10-11	4	11.2	9-12
11-14	6	10.6	4-18

This curve, of course, is incomplete because of the absence of adequate data from birth till 3 years of age. The trend in the rates if continued in the pattern they seem to follow in the earlier years would be to increase as one goes down the age scale, and it would finally be infinity at birth. Therefore, it is obvious that at some point below 3 years of age there must be a leveling off of the rate of secretion. Probably from birth to a few months of age the rate is low. Clinically an infant certainly has an abundance of saliva by 5 to 6 months of age, when the drooling which accompanies the eruption of teeth becomes noticeable. In normal full term infants saliva has been found in the mouth before food is taken.[71] Only small amounts are found at birth, but it is definitely present, as shown by the infant's ability to digest starch. In fact, Nicory [72] has demonstrated the presence of ptyalin in the parotid gland one and one-half months before birth. Mayer has presented some evi-

71. Growth and Development of the Child: II. Anatomy and Physiology, White House Conference on Child Health and Protection, New York, Century Company, 1933.

72. Nicory, C.: Salivary Secretions in Infants, Biochem. J. **16**:387, 1922.

dence [73] that more is secreted by older infants than by younger ones. I have been able to confirm the presence of parotid secretion in newborn babies and in infants up to 4 months of age. The conditions under which saliva from the parotid glands must necessarily be collected in these infants (with jaw retractor in place, etc.) would invalidate any conclusions as to resting rate.

The curves representing the rapid drop in rate of secretion in the younger age groups and the gradual decrease thereafter would seem to

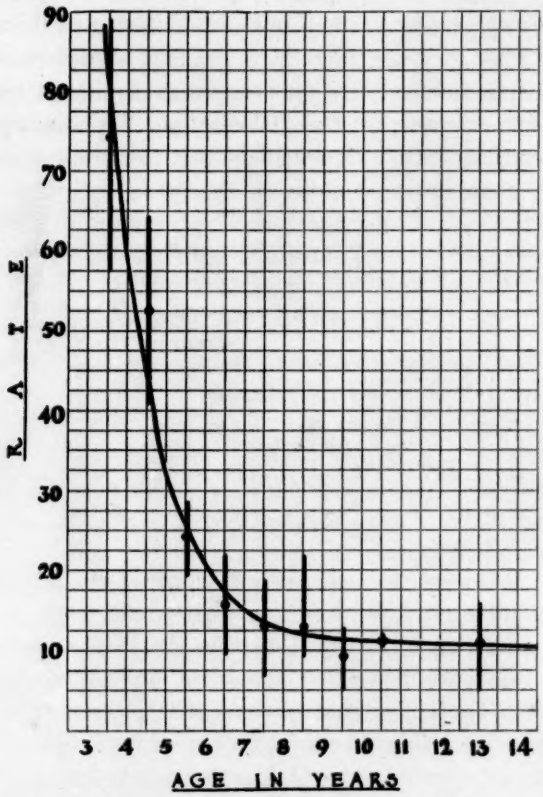

Fig. 2.—Rate of secretion of the parotid glands of normal children. The rate is expressed in terms of 0.01 cc. per five minutes. A-11; k-6.85 per cent per month; the vertical lines indicate the median zone, in which two thirds of the values would be expected to fall, i. e., σ.

represent a function of growth and development. They appear similar to the growth curves obtained in following the development of other body functions, such as heart rate (the slowing of which with age is to

73. Mayer, W. B.: Comparison of Amylase Concentration in the Saliva of Infants and Adults, Bull. Johns Hopkins Hosp. **44**:242, 1929.

some extent a parasympathetic function). One may be allowed to think, therefore, that one is measuring with this curve maturation of the mechanism by which the parotid secretion is mediated, that is, the autonomic nervous system and more particularly the parasympathetic nervous system. However, it cannot be maturation in an anatomic sense that is measured here, because the parasympathetic fibers, which act as the secretory innervation (part III) of the parotid glands, are myelinated at birth. Rather it may be thought of as a maturation of function which becomes evident as the higher centers which affect salivary functioning become sufficiently developed with increasing age to exert their effects on the rate of flow. These midbrain and cortical areas (part III), the presence of which is only sketchily known, may be thought of as directing an inhibitory action on the relatively high rate which would result from the unmodified medullary activity alone.

The few investigators of function of the autonomic nervous system in children have agreed that the child is essentially vagotonic (Pende, Sachs, Eppinger and Hess), becoming gradually less so as he approaches puberty. If one thinks of the rate of parotid secretion as a measure of parasympathetic function, this concept is borne out by my results.

Since in a speculative way the development of cortical activity was mentioned as a possible factor in causing the drop of rate with advancing age in children, it is interesting to compare the curves prepared by Weinbach at Babies Hospital from data compiled by Smith [74] on the development of alpha rhythms in the brain waves of children. When the frequency of alpha waves per second is plotted against age in years, it is found that from a low of 2 waves per second under 1 year of age there is a rapid rise in frequency till about 5 years of age, when a point between 7 and 8 waves per second is reached. From then on there is a more gradual, somewhat uneven rise until after 12 years of age the frequency reaches a point definitely above 9 cycles per second. It will be seen in comparing my figures with these that the increase in alpha rhythms with age is accompanied by a coincident drop in parotid secretory rate. The periods of rapid and then gradual change parallel each other in the measurement of the two functions. In fact, if the curve for change in parotid secretory rate with age is turned upside down, it matches exactly the curve for change in Berger rhythm with age. One has, therefore, an objective measure of the maturation of cortical function which closely parallels the objective measure of the maturation of parotid function, which adds evidence to the hypothesis that it is the development of the influence of the cortex on the lower centers which causes the drop in rate with age.

74. Smith, J. R.: The Electroencephalogram During Normal Infancy and Childhood, J. Genet. Psychol. **53**:455, 1938.

In order to determine the statistical validity of the data presented here, the results were subjected to an analysis of variance according to the method of Fisher.[75] The sources, or variables, included in this analysis were age, sex, restlessness of the subject, minute to minute variation in rate and interindividual differences. Each five minute period was treated separately, and then all the variables were checked over a fifteen minute period. The only significant factor found was the change in rate with age. Restlessness was an apparently somewhat significant factor, but when this too was subjected individually to an analysis of variance it was found to mean only that the restless subjects in any age group were those with the higher rates in that age group and that restlessness had no influence on the change of rate with age.

COMMENT

It has been concluded from parts III and V that there are relationships between the cortex, midbrain and bulbar centers for salivary activity. I have also felt with Foerster [76] that the newborn child is a being in whom only the subcortical centers, thalamus and pallidum, are functioning. It has been postulated that as the child's higher centers mature and exert their inhibitory influence on the lower ones, this increasing ability to inhibit is reflected in the changes in rate of parotid secretion with age. It is an accepted theory that this inhibitory effect of the higher centers is widespread over all subcortical functions. It may be thought of as also having an influence on behavior, which is only a resultant of many factors controlled by the nervous system. This influence on behavior must be reflected at any given age level by the balance between the subcortical and the cortical influences.

With this in mind consider the case of a 10 year old child who cannot apply a check element to his activities, shows evidence of disorganized behavior and has a consistently high rate of parotid secretion, the same as that of a normal 3 year old child. It may be suspected that in such a child the behavior is a reflection of the same failure or delay in maturation represented by the parotid secretory rate. Certainly there is even more reason to suspect that this is true when it is found that children who have normal secretory rates seem to have a better chance to clear up personality disturbances that they may encounter than other youngsters who present similar behavior problems but have abnormal parotid secretory rates.[77]

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75. Fisher, R. A.: Statistical Methods for Research Workers, ed. 5, Oliver & Boyd, London, 1934.

76. Foerster, O.: Antidrome Leitung im sensibeln Nerven, Klin. Wchnschr. **59**:453, 1922.

77. Lourie, R. S.; Barrera, S. E., and Strongin, E. I.: Autonomic Nervous System Function in Children with Behavior Problems as Measured by the Parotid Secretory Rate, Am. J. Psychiat. **99**:419, 1942.

In other pathologic states there is likewise evidence for this correlation between type of behavior and rate of salivary secretion. It is generally agreed that the chronic impulsiveness, aggressiveness and overactivity of the classic postencephalitic patient represent a loss of ability to apply a check to behavior. Witness also in many such patients the drooling of saliva from the mouth. This represents more strictly a regression to a lower level of maturation rather than a delay of maturation.

Another striking example of the relation between regressive disturbances in conduct and parotid activity is to be found in the study of the rate of parotid secretion in schizophrenia by Strongin and Hinsie.[49] Their studies now take on new implications from the present observations on normal children. They reported that the deeper the deterioration, the higher goes the rate. In other words, as the schizophrenic patient regresses to a more infantile level, to the point where he is smearing feces and returning to primtive grasping and sucking reflexes, the rate of parotid secretion too goes back to infantile levels.

The results found by the same authors in depressions of the manic-depressive type may be thought of in the same terms. If, as has been suggested, depressions of this type are the result of the higher brain centers applying an excessive degree of inhibition on lower centers, it is also significant that there is during these depressed states a complete inhibition of activity of the resting parotid glands.

Another point of view from which the results in this study may be evaluated is that of constitutional medicine. Following the terminology of Pende,[64] those children who have a tendency to retain high, or infantile (immature), salivary secretory rates could be thought of as showing hypoevolutism. (Their condition may also be thought of as representing the somatic component of a psychosomatic whole.)

It is interesting to examine Krasnogorski's [78] classification of physiologic types of children in light of the evidence from these results. He has postulated:

1. The central (well balanced) type, in whom the normal infracortical processes are well regulated by the strong cortical activity. These children should and do have normal parotid secretory rates.

2. The subcortical type, in whom the infracortical processes have the upper hand over the cortical influences. In these children the parotid secretory rates are high.

3. The cortical type, in whom the balance is shifted toward a predominance of cortical activity over subcortical activity (anxiety states?). These have comparatively low secretory rates.

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78. Krasnogorski, N.: Physiology of Cerebral Activity in Children as a New Subject of Pediatric Investigation, Am. J. Dis. Child. **46**:473 (Sept.) 1933.

4. The anergic (hypodynamic) type, in whom both the cerebral cortex and subcortical areas are equally hypoexcitable. These children may have any type of rate, depending on superimposed conditions, but it is usually low. Krasnogorski felt that this is the type of child in whom a psychosis develops.

No correlation has been found in this study between rate of parotid secretion and severity of symptoms.

I should like to point out the other directions which the study of the parotid secretory rate in children has taken.

There has become evident in the course of these experiments the existence of a salivolacrimal reflex; with crying there is an increase in parotid secretory rate, and on unilateral olfactory stimulation there is not only an increase in rate of homolateral parotid activity but of lacrimation as well.

In organic neurologic disorders there are indications that the salivary rate may be of some aid in localization of lesions of the brain, tumors, etc.

In differential diagnosis of types of hyperkinetic children the parotid rate has proved of value in picking out children in whom the hyperkinesis may be on the basis of a developmental delay.

In the field of mental deficiency, it has been found that mongolian idiots have normal rates but have the paradoxic rise of rate on concentration that was mentioned earlier. Cretins when not receiving thyroid have low rates and when receiving thyroid have high rates. Familial mental defectives have no characteristic rate but may vary as much as does the population in general, except that possibly they have a higher incidence of increased rates on the whole. All microcephalic children have extremely high rates.

CONCLUSION

The first known use of the salivary secretions as a test is that described by Cannon as having been prevalent centuries ago in certain oriental countries, where the ordeal of rice placed in the mouth of an accused person was used as an indication of fear and therefore of guilt. However, it is only comparatively recently that it was realized how the study of the secretory activity of the salivary glands could be utilized as an aid in physiologic investigations. Especially in the fields of pediatrics and psychiatry it offers the investigator an objective laboratory measure which may be used in the study of psychosomatic reactions. The parotid gland in particular is valuable from this point of view because it is made easily accessible with the aid of a simple laboratory device.

I have gone into considerable detail to describe the technic used in this study of the parotid secretory activity because it was felt to be worth while to record this method, especially since it differs in some fundamental ways from that used heretofore with children.

One fact which has become increasingly evident in researches into the literature on this subject is the considerable use made of translating the results of animal experiments into terms applicable to human beings. This dangerous anthropomorphizing is to blame for much of the confusion and disagreement prevalent among the investigators in the field of salivary activity.

Drs. Nolan D. C. Lewis, S. E. Barrera and Rustin McIntosh, of the College of Physicians and Surgeons, assisted in the general preparations of this study. Dr. A. A. Weech, of Babies Hospital, assisted in formulating and evaluating the problem here investigated; Dr. Joseph Zubin, of Psychiatric Institute, and A. P. Weinbach, of Babies Hospital, rendered assistance in the statistical analyses. Drs. E. I. Strongin and B. Korchin placed their experience in the field of parotid gland reactions at my disposal.

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News and Comment

GENERAL NEWS

Meeting of American Pediatric Society Postponed.—Information has been received from the secretary, Dr. Hugh McCulloch, that the meeting of the American Pediatric Society has been postponed for this year because of war conditions. This is in line with the action of the American Academy of Pediatrics, which likewise has postponed its meetings for the duration of the war.

Dr. Black Honored.—Dr. Arthur P. Black, pediatrician of El Paso, Texas, has received the Sir Henry Wellcome gold medal and cash prize of $500, offered through the Association of Military Surgeons of the United States, for his paper entitled "Measures of Preventive Medicine Recommended by the Federal Medical Services to Insure the Maximum Improvement of the Selectee of 1961 Over Him of 1941," the assigned subject in 1942.

American Board of Pediatrics, Inc.—The dates for the fall examinations have been set. Written examinations will be held locally, under a monitor, on Oct. 8, 1943 and an oral examination, in New York, on November 20 or 21. Further information regarding these examinations may be procured from the secretary, Dr. C. A. Aldrich, Children's Memorial Hospital, 700 Fullerton Avenue, Chicago.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

BACTERIOLOGIC ASPECTS OF SALMONELLOSIS. I. SAPHRA, Arch. de med. inf. **10**:143 (July) 1941.

The author, an authority in the field of salmonella infections, presents a résumé of the present knowledge of the bacteriologic infections. He gives a detailed explanation of the complex problem of the serologic classification of the Salmonella group.

He presents a review of the recent investigations which have been particularly carried out in the Salmonella Center of New York City. These investigations have led to a better understanding and knowledge of the different types of organisms and of the infections that are caused by these bacteria and their widespread presence in the community.

SCHLUTZ, Chicago.

Metabolism; Infant Feeding; Milk and Other Foods

ARTIFICIAL STIMULATION OF LACTATION IN PRIMITIVE CULTURES. H. A. WIESCHHOFF, Bull. Hist. Med. **8**:1403 (Dec.) 1940.

Among primitive peoples nursing is usually carried out for much longer periods than among civilized peoples. It is usually considered essential for the welfare of the child. When the infant's mother dies or becomes unable to nurse and no wetnurse is available, often older women—in many cases the grandmothers—are used as substitutes.

The author has gathered reports about primitive tribes of several continents, some going back as far as the seventeenth century, and shows that the stimulation of breast secretion in older women is no rarity, though it may be long after they have had any children of their own and often many years beyond their menopause. Among many tribes the only stimulation used is the nursing of the infant, but there are many reports of the internal and external use of plant drugs, the latter frequently in the form of poultices. Occasionally massage and beating of the breasts is reported. The information regarding the drugs usually is so sketchy and indefinite as to be of little value, and frequently these treatments are in the hands of native medicine men who carefully guard their secrets.

Most of the reports deal with Africa (South Africa, Southwest Africa, West Africa and Algeria), but there are some from India, Indonesia, Polynesia and North and South America.

The author states that these reports should not be accepted at full value, in particular as all of them lack the proper scientific observations. He believes that with the exception of occasional abnormal secretions women of the age described in these reports are not able to produce milk in sufficient amounts and of the proper nutritional value to nourish infants completely but that the secretion is in the form of colostrum. Infants receive supplementary foods early among these primitive tribes and apparently do not depend entirely on the breast milk.

ROSENTHAL, St. Paul, Minn.

THE STANDARD METABOLISM OF ADOLESCENCE. BRUCE WEBSTER, HELEN HARRINGTON and L. M. WRIGHT, J. Pediat. **19**:347 (Sept.) 1941.

The results of a longitudinal study over a period of five years of the standard metabolism of a group of 13 boys and 8 girls between the ages of 10 and 16 years is described. The average mean variation for the girls was —0.29 calories

per square meter per hour, and for the boys it was + 0.04 calories per square meter per hour. In general, there was a gradual decrease in the relative heat production between the ages of 10 and 16 years. This decrease was most striking between the ages of 11 and 12 years in both the boys and the girls. This was found to be great enough to be statistically significant when tested by the method of Fisher. The boys showed a higher basal metabolism than the girls. This relative increase was present at the age of 10 years, before pronounced skeletal changes due to sexual differences had taken place. The values for basal metabolism of boys obtained in the present study agree closely with those previously reported by Bierring. The values for girls agree almost exactly with those obtained by Kestner and Knipping. The values obtained for both the boys and the girls are considerably lower than the original Aub and DuBois standards. For general clinical purposes it would appear that the Bierring standards for boys and the Kestner and Knipping standards for girls most nearly meet the requirements for normal children of this age period. No evidence of an increase in the average relative heat production at the time of so-called "puberty" was found. The onset of menstrual function in the girls was not associated with a change in relative heat production. The total heat production increases with increasing height and weight. In the girls this rate of increase did not continue after 14½ years. The total calories of the boys continued to increase after 16 years in spite of a marked decrease in growth rate.

RAUH, Cincinnati.

OBESITY IN RELATION TO PUBERTY. HILDE BRUCH, J. Pediat. **19**:365 (Sept.) 1941.

Bruch reports observations made on 200 obese children in all of whom obesity developed before puberty. The excess weight ranged from 25 to 150 per cent. In no patient were there signs of an intracranial lesion. The data presented reveal that obese children are advanced in statural growth and maturation. Early puberal development was the rule for obese girls and was not uncommon for obese boys. Nothing in these observations justified the assumption that obesity in childhood is in any way associated with hypogenitalism or delayed puberty. It was the author's impression that puberty takes a more rapid course in children if they lose excessive fat during adolescence. However, obese boys undergo spontaneous puberty, even if they remain obese or gain weight. Bruch feels that her observations refute all theories which explain obesity in childhood on the basis of hypothyroidism and hypopituitarism. Hypofunction of either of these glands results in retardation of growth and puberal development and not in acceleration of the growth processes. Treatment of the obese child is necessary, not with endocrine substances, but with psychotherapy. The child should be given aid to overcome his personal difficulties, to gain independence from overprotective parents and thus to overcome the habits of overeating and inactivity.

RAUH, Cincinnati.

WHAT TO DO ABOUT THE FAT CHILD AT PUBERTY. F. W. SCHLUTZ, J. Pediat. **19**:376 (Sept.) 1941.

Obesity is seldom a problem in childhood. It usually becomes one at or near puberty. Obesity at puberty may be divided into the endogenous type, in which well defined somatic characteristics and metabolic changes of endocrine dysfunction are present, and obesity of exogenous origin, in which there may be a constitutional element and a familial tendency to obesity. Hormonal factors do not play as important a role in causing adiposity at puberty as is popularly thought. Schlutz suggests four clinical groups for the appraisal of the obese adolescent based on somatic characteristics and laboratory data, such as basal metabolism, tolerance for sugar and blood pressure: true hypothyroid obesity, hypothalamic obesity, frontal lobe obesity and simple exogenous obesity. Treatment of these types is discussed.

RAUH, Cincinnati.

VETERINARY FOOD INSPECTION. ORVILLE E. MCKIM, New York State J. Med. **41**:1433 (July 15) 1941.

This article is part of a symposium on food-borne diseases of the gastrointestinal tract. If shows the protection against possible occurrences of food poisoning available through the use of competent veterinary meat and food inspection. A list of the many diseases which render meat unfit for human consumption is given. Local inspection is necessary to prevent the sale of meat from unsound animals for human consumption. The chief dangers are from tuberculosis, anthrax, tapeworms, actinomycosis, foot and mouth disease and various intestinal disorders.

AIKMAN, Rochester, N. Y.

CYSTINE DIATHESIS. A. HOTTINGER, Ann. pædiat. **156**:257, 1941.

The author describes a case of cystine disease in which the condition was diagnosed during life as dwarfism with renal, hyperphosphatemic rickets. In the course of the illness, symptoms of a storage disease developed. The clinical supposition of the presence of cystine disease made before the death of the patient was confirmed by autopsy. The disease is hereditary. In infancy the symptoms are: anorexia, thirst, nephritis, preuremic conditions, inhibition of growth or dystrophy, rickets and hypophosphatemia. Cystinuria may be missing.

In later childhood one observes: anorexia, nephritis, disturbances of growth, rickets and osteodystrophy with hyperphosphatemia.

In the forms with more favorable prognosis one finds renal concrements with destruction of the kidneys more or less pronounced. In adult life, those forms are prevailing. Cystinuria at this time is more constant than in early childhood. The pathogenesis is supposed to be due to a disturbance in splitting up of a metabolic precursor of the cystine. The consequence is an accumulation of cystine crystals in the reticuloendothelium, inhibition of growth and disturbances of the kidneys.

There is as yet no known treatment.

Many cases reported in the literature as instances of renal rickets with glycosuric dwarfism or nonhealing rickets with glycosuria may be cases of cystine disease.

FROM THE AUTHOR'S SUMMARY.

ANATOMIC PICTURE OF CYSTINE DISEASE WITH DWARFISM. FRED ROULET, Ann. pædiat. **156**:284, 1941.

In cystine disease in childhood dwarfism, deposits of crystalline cystine and an involvement of the kidneys are characteristics. Cystine can be found in hexagonal crystals (diameter up to 10 microns) and in smaller prisms, mostly in intracellular layers. Crystals are enclosed in the sinuses of the lymph nodes and in the pulp of the spleen. It is probable that the crystals enter the cells by phagocytosis caused by the elements of the reticuloendothelial system of the spleen, liver and lymph nodes. The spleen is enlarged in most of the cases and has a multicolored spotted aspect with yellow-whitish stripes, corresponding to the deposits of cystine. The liver is enlarged as well. Small yellow-white triangular spots can be recognized. In Roulet's case, there was much glycogen. The cells filled with cystine are mulberry-like and large (up to 40 microns). Cystine can be overlooked easily because of its solubility in acids, alkalis and solution of formaldehyde. As a fixative, only alcohol is allowed. The author gives two examples of mistakes made by pathologists (Rössle, Benoit). The changes in the kidneys are either nephrotic or, more often, like those of renal dwarfism, an interstitial nephritis with atrophy. Roulet found in his case a chronic interstitial inflammation and a subacute glomerular nephritis too. In the bones, there were signs of rickets combined with symptoms of osteodystrophia fibrosa, mainly lacunar resorption, deformity of the trabeculae by fibrous sprouts of the bone marrow and mosaic-like structures. Similar observations are described in a case of Fanconi's nephrotic glycosuric dwarfism and in the renal osteodystrophy of

adults. The changes in the bones are similar in all cases, without any reference to hyperphosphatemia or hypophosphatemia or to the level of blood calcium. Roulet thinks that the nephrotic glycosuric dwarfism is a step in the development of the cystine disease. He wonders whether cystine diathesis was not overlooked in many cases of renal rickets.

FROM THE AUTHOR'S SUMMARY.

ANALYSIS OF BONES IN A CASE OF CYSTINE DISEASE. E. FREUDENBERG, Ann. pædiat. **156**:335, 1941.

In a case of cystine disease with renal rickets the chemical analysis of the bones showed a defective calcification as expressed by the values of total ash, calcium phosphorus and carbon dioxide.

The head of the humerus was mostly involved. Here was found a deviation of the ratio of residual calcium to phosphorus. The reasons therefor are discussed.

In only a part of the cases of chronic nephritis in childhood are there rickets-like skeletal changes. It is suggested that the development of osseous changes corresponds to the variations of the product Ca × P.

FROM THE AUTHOR'S SUMMARY.

DIAGNOSIS OF CYSTINE DISEASES. MARGRIT ESSER, Ann. pædiat. **156**:344, 1941.

In the difficult diagnosis of cystine disease in childhood sternal puncture is useful. Crystals and cystine can be found in the reticulum cells of smears of the bone marrow.

Smears of bone marrow contained 15.8 per cent of eosinophils, and smears of the blood contained 9 per cent eosinophils. There were no other reasons for this augmentation than the cystine disease.

There was no increase of reticulum cells of the bone marrow, in distinct contrast to the behavior of bone marrow in the cases of lipoidosis.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

THE RELATION OF NUTRITION TO GASTRIC FUNCTION: III. THE EFFECT OF VITAMIN B_1 DEFICIENCY. HELEN M. DYER and JOSEPH H. ROE, Am. J. Digest. Dis. **7**:329 (Sept.) 1941.

This research problem, with the albino rat as the subject, indicates that acute or chronic deficiencies of thiamine vitamin (B_1) have no pathologic effect on the gastric juice–secreting cells. Since a diminished response to gastric stimulation does not occur until the animals are moribund and the diminished response of moribund animals is promptly overcome by thiamine hydrochloride therapy, it would appear that no serious damage to the secreting cells of the gastric mucosa occurs even with conditions of extreme deficiency.

In examining these rats at autopsy, the only striking difference observed between the control rats and the thiamine-deficient animals was the extreme amount of storage fat in the former and the complete absence of fat deposits in the latter. The gastric mucosa was normal in appearance in 14 of the control adult rats, in 12 of the adult rats which showed only mild symptoms and in 8 of the animals which showed severe symptoms of the vitamin deficiency. In 2 normal adults and in 8 of the thiamine-deficient rats, petchial hemorrhages were found in the gastric mucosa midway between the forestomach and the pylorus.

MOMSON, Savannah, Ga.

THE RENAL EXCRETION OF INORGANIC PHOSPHATE IN RELATION TO THE ACTION OF VITAMIN D AND PARATHYROID HORMONE. HAROLD E. HARRISON and HELEN C. HARRISON, J. Clin. Investigation **20**:47 (Jan.) 1941.

In their studies on the role of the kidneys in the regulation of the concentration of phosphate in the body fluids, Harrison and Harrison have made important

contributions to the knowledge of the physiologic action of vitamin D. Their findings offer new explanations of older data on the phosphorus metabolism in rachitic infants and experimental animals. Reabsorption of phosphate by renal tubules was studied quantitatively by concurrent determinations of creatinine and phosphate clearances in dogs following intravenous injections of phosphate salts. The administration of vitamin D to young dogs fed a rachitogenic diet produced a marked increase in the maximal rate of reabsorption of phosphate by the renal tubules. This effect was demonstrable twenty-four hours after adequate amounts of vitamin D were given. Parathyroid extract had an effect opposite to that of vitamin D.

GUEST, Cincinnati.

INFLUENCE OF HYPERPYREXIA ON ASCORBIC ACID CONCENTRATION IN THE BLOOD. STAFFORD L. OSBORNE and CHESTER J. FARMER, Proc. Soc. Exper. Biol. & Med. **49**:575 (April) 1942.

Seventeen patients with chronic arthritis in a total of 77 observations were found to have no essential change in the plasma ascorbic acid level when hyperpyrexia (temperature of 104 F. [rectal] for four hours) was induced by means of a combination of fever cabinet and inductotherm.

HANSEN, Minneapolis.

Hygiene; Growth and Nutrition; Public Health

GENERAL CONSIDERATIONS: CERTAIN PROBLEMS OF PUBERTY AND ADOLESCENCE. LAWRENCE K. FRANK, J. Pediat. **19**:294 (Sept.) 1941.

Puberty, or the first stage of sexual maturation, begins in the age period around 9 to 10 years, when an acceleration of developmental processes occurs. The period following this first stage in maturation may be regarded as the period of adolescence and may extend on into the end of the second decade or even into the third decade. The menarche represents only the first stage of sexual maturation in the female, and the later stage of actual ovulation may not occur for one, two or three years after the menarche. It must be recognized that during the period of puberty and adolescence there is an orderly sequential process of growth, development and maturation, but each boy and girl will pass through this sequence at his or her own rate of progress and with structural and functional dimensions that are peculiar to his or her constitution and heredity. However, adolescence may be a period of organic incongruity in which, for example, full adult stature may be attained in a relatively short time but development of the cardiovascular, gastrointestinal and muscular system, and gonadal development and emotional makeup may remain immature and mature at a much slower pace. This organic imbalance or asymmetric growth will give rise to many defects, maladjustments and instabilities which must be understood and treated. Frank points out some of the difficulties which result from this organic imbalance and stresses the function of the pediatrician in caring for the adolescent in the schools, camps, and other groups to which the adolescent belongs.

RAUH, Cincinnati.

EXAMINATION OF THE ADOLESCENT FEMALE. JOSEPH L. BAER, J. Pediat. **19**:315 (Sept.) 1941.

Baer enumerates and discusses the abnormalities and pathologic conditions which the pediatrician must keep in mind when examining the adolescent female. In addition to routine inspection of the genitalia, a rectoabdominal examination of the genitals should be included in the physical examination. The pediatrician should become familiar with the size and shape of the developing normal uterus and should be able to detect hematometra and hematocolpos. He should learn to recognize a retrodisplaced uterus and distinguish between retroversion and retroflexion. Treatment of an imperforate hymen is outlined. A discussion of vaginal discharge, its causes and treatment is included.

RAUH, Cincinnati.

DEMOCRACY AND POPULAR SCHOOL (ARGENTINA). LUIS MORZONE, Bol. Inst. internac. am. de protec. a la infancia **15**:191 (Oct.) 1941.

The educational culture which belongs to people should embrace three periods: primary school, popular school and professional school.

The first should be organized as an instrument for the acquirement of civil knowledge. The second should exist to accomplish the development of the mind and should be appointed to provide the multitudes with the knowledge and principles of the abilities necessary to participate in the aims of a population and thus contribute to the development of national and human life. The third is called on to give technical social value to pupils' vocations and thus build up all the facets of personality.

FROM THE AUTHOR'S CONCLUSIONS.

MEDICAL CERTIFICATE FOR ENTRANCE TO PRIMARY AND SECONDARY EDUCATIONAL ESTABLISHMENTS (BOLIVIA). JULIO CÉSAR PÉREZ, Bol. Inst. internac. am. de protec. a la infancia **15**:217 (Oct.) 1941.

In the first place the author refers to the urgent necessity for Bolivia to intensify protection of mothers and children, especially during preschool age, so that children at their entrance to school will be in a better physical, mental and spiritual state.

Following that idea, he emphasizes the importance of establishing as an essential requirement the obtaining of a medical certificate before the entrance to the primary and secondary educational establishments, whether they are public or private. The certificate ought to be given by the school health authorities. This would be a preventive measure of great value for Bolivia, where the people, on account of being deficiently fed and also on account of unhygienic environments, are prone to have multiple contagious diseases, in particular, tuberculosis and syphilis in their diverse forms.

FROM THE AUTHOR'S SUMMARY.

NEED OF WIDESPREAD FEMININE COOPERATION IN THE FIGHT AGAINST INFANT MORTALITY. Bol. Inst. internac. am. de protec. a la infancia **15**:250 (Oct.) 1941.

The Venezuelan Women's Association at the end of the present statement makes the following suggestions:

1. To solicit the collaboration of all the people who have taken part in this congress (Second Venezuelan Child Congress) so as to thoroughly prepare the Venezuelan women in child care, hygiene and psychology, each one according to her capacity.

2. To urge the competent organizations, the state in its corresponding department and the women's associations to develop systematically and constantly the teaching of child care.

3. To recommend to mothers, future mothers, students and school girls the organization of child care courses or their application, in order that such courses may be established in the places where they live, and in that way widely spread the knowledge thus acquired to every Venezuelan woman ignorant of it.

FROM THE AUTHOR'S CONCLUSIONS.

Newborn

PHYSIOLOGY AND ANATOMY OF THE RESPIRATORY SYSTEM IN THE FETUS AND NEWBORN INFANT. WILLIAM F. WINDLE, J. Pediat. **19**:437 (Oct.) 1941.

Windle first discusses the chemical factors in fetal respiration, namely, the factors which control the saturation of oxygen in the umbilical vein. The mechanism for respiration in the fetus is developed early in embryonic life. The somatic motor system develops first and soon thereafter the nervous mechanism. The respiratory mechanism of the fetus is developed long before it can be of any use.

Windle cites experiments to demonstrate how easy it is to alter the physiologic state of the fetus in utero and to start respiratory movements. Partial anoxemia usually results in heightened excitability of the fetal respiratory center, and its neurons begin to discharge in response to the usual factors which are stimulatory in the adult. Respiration begins at birth because the excitability of the center increases as anoxemia builds up during placental separation. Rhythms of shallow, rapid respiratory movements which are occasionally seen late in gestation signify that the fetus is momentarily experiencing an elevation of excitability of its center or an elevation of blood carbon going to the brain. A physiologic partial anoxemia may occur toward the end of gestation as the result of progressive decline of placental efficiency; with this, minor rhythms of fetal respiratory movements are occasionally seen. These movements are rarely encountered and when observed should give cause for apprehension. Aspiration of amniotic fluid is not a normal phenomenon; it occurs only under conditions of marked anoxia.

RAUH, Cincinnati.

THE INFLUENCE OF THE DIET OF THE NEWBORN INFANT ON THE PROTHROMBIN INDEX. S. S. GELLIS and R. A. LYON, J. Pediat. **19**:495 (Oct.) 1941.

The prothrombin indexes of four groups of newborn infants were influenced by the type of feeding offered during the first few days of life. The group of infants fed at the breast every four hours, beginning twelve hours after birth, showed the greatest decline in their prothrombin indexes and the most prolonged recovery to initial levels. The group of infants who received bottle feedings of fully formed breast milk after each breast feeding on the same time schedule showed a less marked drop in their prothrombin indexes and a more rapid recovery than the first group. Better results were obtained in a third group of infants, who received additional feedings of evaporated milk started thirty-six hours after birth. The group of infants who received additional feedings after each nursing, beginning twelve hours after birth, showed the least decline in prothrombin indexes and the most rapid recovery to normal values. In studies of the behavior of the prothrombin index of the newborn infant, it is important to record the type and schedule of feeding so that the results of one observer may be compared accurately with those of another. RAUH, Cincinnati [AUTHORS' SUMMARY].

PROTHROMBIN IN THE NEWBORN INFANT: IV. FURTHER OBSERVATIONS ON THE PROTHROMBIN RESPONSE TO INTRAVENOUS ADMINISTRATION OF WATER-SOLUBLE NAPHTHOQUINONE. SIMON KOVE and HENRY SIEGEL, J. Pediat. **19**:513 (Oct.) 1941.

Ten newborn infants exhibiting various degrees of prothrombin deficiency were given 2 mg. of 2-methyl-1,4 naphthoquinone (menadione) intravenously. Determinations of prothrombin (Quick's methods) were made after one-half, one, one and one-half, two, three and twenty-four hours. Within one and one-half hours after the injection each infant showed a definite elevation of prothrombin. Within twenty-four hours the prothrombin concentration was within the normal range, of 70 to 100 per cent, and it was maintained at such a level for several days thereafter. In a previous investigation the authors found an elevation of prothrombin within one to two hours following the intravenous administration of 1 mg. of naphthoquinone. They conclude that a dose of 1 mg. is adequate and that 2 mg. is probably more than is necessary. In addition, they found that there is no relationship between the severity of hypoprothrombinemia and the rapidity of the initial prothrombin response.

RAUH, Cincinnati.

CALORIE REQUIREMENTS OF FULL-TERM AND PREMATURE INFANTS IN THE NEONATAL PERIOD: A FORMULA. ITS USES AND LIMITATIONS. HELEN M. M. MACKAY, Arch. Dis. Childhood **16**:166 (Sept.) 1941.

A formula is suggested whereby the food intake of a newborn baby may be regulated. According to this the baby should receive on the first day of life

calories equivalent to $\frac{1}{7} \times 50 \times$ birth weight in pounds, and his feedings should increase by this same amount each day of the first week, so that by the seventh day of life he would be given 50 calories per pound of birth weight. It is pointed out that the formula overestimates the intake of normal breast-fed babies during the first two days, when breast secretion is scanty. In the second week of life 50 calories per pound of birth weight is taken as the usual requirement. The importance is emphasized of using these figures simply as guides and not to enforce a rigid system of feeding.

It is assumed that the average value of human colostrum and milk during the first two weeks is 20 calories per fluidounce. One hundred and seven premature babies who had their food intakes checked to the formula made good progress.

All artificial feedings were given in a strength to provide 20 calories per fluidounce. The fluid intake was augmented by giving water.

KELLY, Milwaukee.

PERIUMBILICAL STAPHYLOCOCCUS ERYSIPELAS IN A 20 DAY OLD INFANT. A. ZANINI, Med. ital. **21**:505 (Dec.) 1940.

The author describes the case of a 20 day old infant who acquired staphylococcic erysipelas of the umbilicus and after thirty-five days died of bronchopneumonia. The author reviews 29 cases of staphylococcic erysipelas, in 23 of which the patient died. The initial lesion was localized around the nose or upper lip.

MARTOCCIO, Utica, N. Y.

Acute Contagious Diseases

CLINICAL STUDIES IN IMMUNITY TO PERTUSSIS WITH THE USE OF PERTUSSIS SKIN TESTING TOXIN AND ANTIENDOTOXIN. L. P. STREAN, D. LAPOINTE and E. DECHENE, Canad. M. A. J. **45**:326 (Oct.) 1941.

One hundred children at LaCreche, Quebec, Canada, were picked at random and tested intradermally with 0.1 cc. of pertussis toxin, representing $\frac{1}{15}$ of a mouse minimum lethal dose.

The children fell into three groups: Group I was composed of 20 children under 6 months of age with no previous history of pertussis; 65 per cent of them reacted positively. Group II included children over 6 months and under 5 years of age with no previous attack of pertussis. Group III included 34 children of all ages up to 4 years who gave a history of having had pertussis; 26 per cent of them showed positive reactions.

Several months later an epidemic of pertussis developed in the ward; none of the children who had negative reactions to the cutaneous test contracted the disease during this outbreak.

Treatment was by use of antiendotoxin or antibacterial serum or both.

In cases in which antiserum was effective, the cutaneous reaction became negative twenty-four hours after the serum was injected.

The authors feel that the combination of the antiendotoxin and the antibacterial serum was preferable in treatment to either alone.

MOORE, Omaha.

HIGH INCIDENCE OF INFECTIVE STOOLS IN A SMALL OUTBREAK OF INFANTILE PARALYSIS. GEORGE Y. MCCLURE, J. Lab. & Clin. Med. **26**:1906 (Sept.) 1941.

The author produces further evidence of the infective nature of the stools from persons with anterior poliomyelitis. Though the epidemic was a small outbreak, it provided the author with material for several rather interesting remarks in his paper. One is that a stool specimen collected as late as forty days after probable onset of disease was found to be infective. The other pertains to the resistance of the virus if kept at low temperatures; it was found that stool remained infective one hundred and twenty-four days after collection. From stools of the 17 patients studied, only 5 "takes" were obtained in laboratory monkeys.

GARD, Galveston, Texas.

MENINGOCOCCEMIA WITHOUT MENINGITIS. LESTER D. WATSON, New England J. Med. **225**:685 (Oct. 30) 1941.

The author's case, reported in detail, concerned a 55 year old woman who was admitted to the hospital on Feb. 29, 1940, complaining of chills and fever, maculopapular lesions on the face, trunk and extremities and pains in the joints.

A blood culture positive for meningococci was obtained on March 7. Thirty grains (2.0 Gm.) of sulfanilamide was given at once, followed by 20 grains (1.3 Gm.) every four hours. The blood sulfanilamide level was maintained between 11.8 and 14.3 mg. per hundred cubic centimeters from March 7 until March 15, although medication was reduced gradually from March 11 because of rapid improvement.

She was discharged from the hospital on March 23 without symptoms, twenty-three days after admission and thirty-seven days after onset. One year later the patient was in excellent health.

The author's summary and conclusions are as follows:

"The literature on meningococcemia without meningitis is reviewed, and an additional case is reported. The diagnosis was obscure until verified by blood cultures in the third week of disease. All symptoms rapidly disappeared following sulfanilamide treatment.

"The patients in the sulfonamide-treated cases of the disease thus far reported in the literature have all completely recovered promptly without sequelae.

"Meningococcemia should be considered in any patient presenting symptoms of intermittent fever, unexplained rash and arthralgia." GENGENBACH, Denver.

AN EPIDEMIOLOGICAL STUDY OF POLIOMYELITIS IN MISSISSIPPI in 1941. L. L. LUMSDEN, Pub. Health Rep. **57**:729 (May 15) 1942.

This study includes 148 cases, with 19 deaths. The incidence per hundred thousand of population was 8.9 white and 5.8 Negro. The greatest age incidence was under 5 years, with the 5 to 9 year old group next, followed by the 10 to 14 year old group. The greatest seasonal incidence was in May, June and July. The epidemiologic evidence was that the disease was spread not by personal contact but by unknown factors. These factors included rats, birds, domestic fowls, bovines, house flies, horse flies, blow flies, mosquitoes, fleas or other insects as vectors and tended to operate with striking localization. On the whole, a picture was presented of spread of infection by place rather than by person.

SANFORD, Chicago.

THE MANZULLO TEST IN THE EARLY DIAGNOSIS OF DIPHTHERITIC ANGINA. ABRAMO GIORGETTI, Med. ital. **21**:497 (Dec.) 1940.

The Manzullo test consists in touching the membrane in the throat with a solution of 2 per cent tellurite. There results a blackening of the membrane if it is diphtheritic. The author studied 130 subjects, of whom 111 had definite diphtheria by bacteriologic examination and 19 had angina with an exudate. The author concludes that the test is nonspecific, but for a physician who is situated far away from a well equipped laboratory this test can be of some value, because in a large number of cases the result of this test agrees with that of the bacteriologic examination when it is positive for diphtheria.

MARTOCCIO, Utica, N. Y.

IMMUNITY AGAINST DIPHTHERIA AND TETANUS IN ANIMALS. E. BEHRING and U. KITASATO, Med. ital. **22**:4 (Jan.) 1941.

This is a reprint in Italian of the original article by Behring and Kitasato which appeared in the *Deutsche medizinische Wochenschrift* for Dec. 4, 1890. It is reprinted in honor of the fiftieth anniversary of the discovery of serum therapy.

MARTOCCIO, Utica, N. Y.

IMMUNITY AGAINST DIPHTHERIA IN ANIMALS. E. BEHRING, Med. ital. **22**:7 (Jan.) 1941.

This is a reprint from the *Deutsche medizinische Wochenschrift* for Dec. 11, 1890. It is reprinted in honor of the fiftieth anniversary of the discovery of serum therapy.

MARTOCCIO, Utica, N. Y.

TREATMENT OF DIPHTHERITIC CROUP. F. TECILAZIC and A. MAGGIO, Med. ital. **22**:12 (Jan.) 1941.

There are reviewed 975 cases of diphtheritic croup from 1932 to 1938. The age distribution, sex incidence, and mortality among the various age groups are discussed. The importance of direct laryngoscopy as a diagnostic aid is stressed, as is also the necessity for aspiration of the membrane during laryngoscopy. The mortality of diphtheritic croup is lowered by early serum therapy. Polyvalent antipneumococcus serum does not prevent the appearance of bronchopneumonia.

MARTOCCIO, Utica, N. Y.

MALIGNANT DIPHTHERIA. J. L. LEUNDA, Arch. argent. de pediat. **11**:3 (Jan.) 1940.

The author states that the biologic properties of the Löffler bacillus do not always explain the extremely toxic picture of malignant diphtheria. Constitutional factors play a fundamental role in the causation.

Malignant diphtheria is always primary. The clinical picture is characteristic and easily establishes the diagnosis. The evolution of toxic diphtheria is irregular.

Prognosis of malignant diphtheria is always grave but is conditioned in general by the toxicity of the picture, the development of hemorrhagic manifestations, the age of the child and the promptness with which treatment is begun. Serum therapy must be given early and in an adequate amount; even so it is not always effective against malignant diphtheria.

In malignant diphtheria there are polyvisceral tissue, humoral, hormonal and vitamin factors involved.

In the treatment of malignant diphtheria these factors must be taken into account. Immunization against malignant diphtheria protects against this condition quite as effectively as it does aganist nonmalignant diphtheria and certainly modifies the disease and can prevent it entirely.

SCHLUTZ, Chicago.

ESTIMATIONS OF THYROID HORMONE IN INFECTIOUS DISEASES. STEPHAN ZIMÁNYI, Ann. pædiat. **156**:357, 1941.

The changes in the thyroxin content of the blood serum and even more its coordination with the different stages of infection show that the increase of thyroxin of the serum has the same course as the reaction of the organism against infection and is in intimate connection with the development and growth of resistance.

AUTHOR'S SUMMARY.

IMMUNITY FOLLOWING SCARLET FEVER. FRIEDERIKE BARTH and E. FREUDENBERG, Ann. pædiat. **157**:369 (Dec.) 1941.

Of 1,200 cases of scarlet fever in 19 there were clinically certainly two attacks. The period between the first and the second infection ranged from five months to seven years. The majority of the double infections were in children up to 6 years of age.

Examination at the end of the sixth week with the Dick test showed 47 per cent of 303 children convalescing from scarlet fever still having positive reactions.

The younger children predominate among those giving positive reactions, and the acquiring of negativity can be expected in three fourths of the cases after the tenth year.

The blood serums of the majority of the children with positive Dick reactions showed no Schulz-Charlton phenomena, while the majority of those with Dick-negative serums had extinction phenomena. No child under 6 years had extinction potential in its serum at the end of the sixth week of infection.

Our observations disprove that immunity to scarlet fever is definite at the end of the sixth week in children under 10 years of age. Immunity is often too highly valued.

The reduction in the frequency of the positive Dick reactions at the end of the sixth week of infection with increasing age, the frequency of two attacks in children between 3 and 6 years of age and finally the increase in the attainment of the extinction potential of the serum with increasing age show that it is not so much the survival from the infection as the maturing of the child and helps toward immunity. The Färör epidemic demonstrated this too.

AUTHORS' SUMMARY.

SEROUS MENINGITIS, ULCERATIVE STOMATITIS AND INFECTIOUS ARTHRITIS WITH EPIPHYSIOLYSIS OF THE LEFT HIP JOINT IN SCARLET FEVER. F. BUSER, Ann. pædiat. **158**:110, 1942.

The author reports a case of very toxic scarlet fever complicated with a serous meningitis, an ulcerative stomatitis and a severe long-lasting nonsuppurative monarthritis with epiphysiolysis of the hip joint.

AUTHOR'S SUMMARY.

INFLUENCE OF HIGH ALTITUDE FLIGHTS ON CHILDREN WITH WHOOPING COUGH. BRIGITTE KUJATH, Arch. f. Kinderh. **118**:140 (Dec. 19) 1939.

Thirty-one children who were hospitalized for whooping cough were taken in an airplane to a height of 3,500 meters (10,500 feet) within half an hour; they remained at that height for one hour and then were flown down within half an hour. In but 3 children an improvement was noticed as regards the number and the severeness of the attacks. Complications in the lungs or the heart were not influenced at all. The results are regarded as negative. There may be a psychic influence, especially in neuropathic children with a psychogenic residual.

ARON, Chicago.

HISTORY OF SMALLPOX INOCULATION BEFORE EDWARD JENNER. B. J. GOTTLIEB, Med. Welt **13**:1466, 1939.

Gottlieb gives an interesting history of smallpox inoculation, the knowledge of which dates back to the publication of Emanuele Timoni's "Historia variolarum quae per insitionem excitantur" in Constantinople in 1713. From ancient sources he cites two directions for performing the inoculation (after A. v Haller and S. A. A. D. Tissot).

ISOLATION OF A VIRUS FROM A CASE OF ACUTE POLIOMYELITIS IN PEIPING, WITH HISTOPATHOLOGICAL STUDIES. C. H. YEN and Y. K. HSU, Chinese M. J. **60**:199 (Sept.) 1941.

Reports of epidemics of poliomyelitis in China are few as compared with reports for America and Europe, one of the early ones being 1913. The authors therefore consider it worth while to report their recent case, with the isolation of the strain of the virus for comparison with the strains that have been isolated in other countries. The poliomyelitis occurred in an American girl aged 10 years admitted to the Peiping Union Medical College in 1940. She had lived in Peiping continuously since the age of 6 months. Death occurred on the fourth day of the disease. The high cell count in the spinal fluid was chiefly neutrophilic, and the high intracranial pressure suggested at first a meningococcic meningitis, for which sulfanilamide was used without effect. The child was placed in a respirator, without improvement.

Tissue taken at autopsy from the brain and the cord was used for inoculation of certain animals without producing any infection during the first two months of the trial. The glycerinated material was kept in the refrigerator for five months and then injected into a monkey, which took sick four days later; fever developed on the fifth day and paralysis of the extremities on the sixth day; death occurred on the seventh. This shows an incubation period of four days. Spinal fluid from the animal was cloudy and contained 606 lymphocytes and 340 red cells. The minute changes of the nervous system resembled those of the human patient, although there was less severe degeneration of the parenchyma. In both the child and the monkey the picture was that of acute poliomyelitis of the cord and brain stem, the nuclei of the cerebellum and the precentral gyrus of the cerebrum.

NEFF, Kansas City, Mo.

Acute Infectious Diseases

OBSERVATIONS ON THE EFFECT OF STREPTOCOCCAL UPPER RESPIRATORY INFECTIONS ON RHEUMATIC CHILDREN: A THREE-YEAR STUDY. ANN G. KUTTNER and ELMA KRUMWIEDE, J. Clin. Investigation **20**:273 (May) 1941.

In each of three outbreaks of streptococcic infections of the upper respiratory tract in a colony of rheumatic children during three successive winters a single type of group A beta hemolytic streptococci was found, but during each epidemic a different type was prevalent. A comparison of the epidemic strains and of the rheumatic histories of the children who escaped and the children who had rheumatic recurrences disclosed no striking differences. No rheumatic recurrences were observed in children who escaped streptococcic infections of the upper respiratory tract during the three year period.

GUEST, Cincinnati.

INVESTIGATION OF PROTECTIVE ANTIBODIES PRODUCED BY ORAL ADMINISTRATION OF TYPHOID VACCINE. H. D. MOORE and LUCILLE BROWN WALKER, J. Lab. & Clin. Med. **26**:1583 (July) 1941.

In cooperation with the Army Medical School, Moore and Walker gave 25 adults oral doses of typhoid vaccine. They were given 3 capsules of 10,000,000,000 heat-killed bacilli. The agglutinins were tested at two weeks and six weeks after vaccination. By six weeks nearly all subjects showed a high titer. These investigators feel that the oral method of administration may be possible, but they do not advise its use at the present time.

GARD, Galveston, Texas.

SENSITIZATION INDUCED BY TETANUS TOXOID, ALUM PRECIPITATED. HERMAN GOLD, J. Lab. & Clin. Med. **27**:26 (Oct.) 1941.

The author reviews the literature concerning reactions to alum-precipitated tetanus toxoid. He discusses the use of routine cutaneous tests before the injection of tetanus toxoid, but he feels that such tests would have little practical value. They would serve only to make a simple and effective method of immunization against tetanus a difficult cumbersome one. He describes three types of reaction on second and third injections of tetanus toxoid: acute anaphylactic reaction, definite constitutional symptoms and local reaction only. Two types of cutaneous reactions are obtained: an immediate erythema and a delayed reaction, which consists of erythema, induration, papule formation and local swelling, reaches its height in about twenty-four hours and then subsides gradually. It has been noted that the ability of the material to produce a reaction depends to some extent on the medium on which the tetanus bacillus was grown. The author also gives evidence to indicate that sensitization to toxoid protein or bacterial protein in the immunizing material may also occur on the injection of the alum-precipitated tetanus toxoid. The author is unable to explain the discrepancy between the high

incidence of positive reactions to cutaneous tests and the low incidence of clinical manifestations of allergy following the injection of alum-precipitated toxoid.

GARD, Galveston, Texas.

NEUROTROPIC VIRUS DISEASES OF MAN. ALBERT B. SABIN, J. Pediat. **19**:445 (Oct.) 1941.

Sabin presents a brief résumé of some of the present knowledge of the neurotropic virus diseases of man. The diseases are divided into epidemic and nonepidemic groups. Poliomyelitis and the five varieties of encephalitis (lethargica, St. Louis, Japanese type B, eastern equine and Australian "X") are included in the former group. Among the nonepidemic diseases are lymphocytic choriomeningitis, pseudolymphocytic choriomeningitis, western equine encephalitis, rabies, louping ill, "B" virus disease, herpes simplex, herpes zoster and acute nonsuppurative encephalitis (of unknown etiology). A brief description of the epidemiology of these diseases is given. Sabin's table summarizes the characteristics of the eleven viruses known to affect the human nervous system:

Some Properties of Viruses Affecting the Human Nervous System

Virus	Pathogenicity for Usual Laboratory Animals *				Approximate Size (Mu)	Inclusions
	Rhesus Monkeys	Mice	Guinea Pigs	Rabbits		
Poliomyelitis	+	0	0	0	10	Intranuclear; type B
Encephalitis (St. Louis)	0 to ±	+	0	0	25	0
Encephalitis (Japanese)	±	+	0	0	Small	0
Louping ill	+	+	0	0	17	0
Lymphocytic choriomeningitis	+	+	+	0	50	0
Pseudolymphocytic choriomeningitis	±	+	0 or ±	0	185	0
Equine encephalitis (eastern)	+	+	+	+	25	Intranuclear; type B
Equine encephalitis (western)	+	+	+	+	25	Intranuclear; type B
Rabies	+	+	+	+	125	Cytoplasmic; Negri bodies
"B" virus	+	0 to ±	0 to ±	+	125	Intranuclear; type A
Herpes simplex	0	+	+	+	125	Intranuclear; type A

* The pathogenicity indicated in this table is for the viruses as they are found in human tissues, body fluids, secretions or excretions.

RAUH, Cincinnati.

MISCELLANEOUS NOTES ON RATBITE FEVER: REPORT OF TWO CASES; REVIEW OF AMERICAN REPORTS FROM 1931 TO 1940; OBSERVATIONS ON THE ISOLATION OF SPIRILLUM MINUS, AND RESULTS OF STANDARD SEROLOGIC TESTS DURING RATBITE FEVER. PAUL V. WOOLLEY JR., J. Pediat. **19**:513 (Oct.) 1941.

Two cases of ratbite fever are reported. A review of American cases reported since 1931 is given, with the addition of 33 instances of infection, bringing the total number of reported cases for this country to 110. The technic of isolating Spirillum minus is discussed. The direct examination of bodily fluids has given satisfactory results in only a few instances. Inoculation of blood or lymph node juice into animals, preferably guinea pigs, has proved of most value for isolating the organism. If blood is used, most satisfactory results will be obtained if the blood is withdrawn during a febrile episode and immediately injected into the animal. The precipitin type of serologic reaction, such as that of Kahn or Hinton, is positive in about 90 per cent of cases by the end of the fourth week, while the Wassermann reaction is usually negative. The positive reaction to a precipitin test becomes stronger after the fourth week and fades with conclusion of adequate therapy.

RAUH, Cincinnati.

EPIDEMIOLOGY OF FOOD-BORNE DISEASES OF THE GASTROINTESTINAL TRACT. JAMES E. PERKINS, New York State J. Med. **41**:1438 (July 15) 1941.

This paper, part of a symposium, gives an excellent review of trichinosis, amebic dysentery, bacillary dysentery, typhoid fever, botulism, staphylococcus toxin food poisoning, poisoning from filtrable viruses and poisoning from chemicals.

AIKMAN, Rochester, N. Y.

SPONTANEOUS ORNITHOSIS (PSITTACOSIS) IN CHICKENS THE CAUSE OF HUMAN INFECTION. K. F. MEYER and B. EDDIE, Proc. Soc. Exper. Biol. & Med. **49**:522 (April) 1942.

The 54 year old wife of a poultry farmer acquired an acute febrile illness which was believed to be psittacosis. The patient's serum gave a strongly positive reaction in the complement fixation test for psittacosis in dilutions of 1:32 on the twelfth and 1:128 on the forty-first and one hundred and fifty-fifth days. Study of the chickens, 500 of which had died during the preceding year, indicated these fowls to be the source of the infection. The husband and two children gave specific complement fixation reactions in dilutions of 1:4 and 1:8. The reactions of the 7 year old son were negative.

HANSEN, Minneapolis.

A TRANSVERSE LESION OF THE SPINAL CORD FOLLOWING ANTI-TETANUS SERUM THERAPY GIVEN INTRASPINALLY. I. SERRA, Med. ital. **22**:34 (Jan.) 1941.

The author describes the case of a 12 year old boy who was given tetanus antitoxin intraspinally for tetanus. He was discharged as cured after sixteen days in the hospital. Eight days after discharge serum sickness developed with hives and articular pains but no elevation of temperature. Two attacks of serum sickness developed. He was returned to the hospital about two months after discharge because of weakness of both lower extremities and inability to walk. Active motion of the lower extremities was absent. There was no spasticity on passive motion. Sense of touch, heat and of pain were absent, which indicated a lesion in the sixth and seventh dorsal segments. Upper abdominal reflexes were present but diminished; lower abdominal and cremasteric reflexes were absent. Ankle and knee jerks were hyperactive. Ankle clonus was present. Babinski and Oppenheim reflexes were absent. Painful stimulation of the skin of the lower extremities caused a rapid flexion of the limb. The Wassermann reaction was negative, and roentgenograms of the chest and spinal column showed no abnormalities. Lumbar puncture gave a dry tap. The author concludes that the syndrome was due to a circumscribed arachnoiditis followed by a slow and progressive compression of the cord.

MARTOCCIO, Utica, N. Y.

OCCURRENCE OF RHEUMATIC DISEASE WITH AND WITHOUT CARDIOPATHIES IN THE HOSPITAL OF BUENOS AIRES DURING THE YEAR 1938. J. M. MACERA, A. P. RUCHELLI and R. GAIG, Arch. argent. de pediat. **13**:38 (Jan.) 1940.

The authors believe that acute rheumatic disease of childhood is a serious disease. Of the 1,110 cases observed in Buenos Aires, in 649 there were evident cardiopathies.

Argentina, like many other countries, has a high proportion of morbidity and mortality (22 per cent mortality due to cardiopathies). This proportion is higher than in many other nations.

The authors suggest the organization of a campaign for prophylaxis in childhood, especially during the first decade or so of life, since it is during this period that so many of the cardiopathies first manifest themselves. They advise the establishment in all pediatric clinics of a special clinical service for rheumatic and cardiac diseases.

SCHLUTZ, Chicago.

CLINICAL ASPECTS OF THE SALMONELLOSES. A. A. ABALLI, Arch. de med. inf. **10**:158 (July) 1941.

The author presents a series of reports which demonstrate the enormous importance, seriousness and frequency of salmonella infections in children as they have been observed in the Municipal Hospital in the city of Habana, Cuba.

Statistical material of his own records shows that the incidence of these infections is far greater than is generally believed and that routine bacteriologic examinations in the study of the etiologic gastroenteric diseases, especially the bacillary types, will confirm his statements.

SCHLUTZ, Chicago.

COMPLICATIONS IN THE CENTRAL NERVOUS SYSTEM IN MALARIA IN CHILDHOOD. A. ECKSTEIN, Ann. pædiat. **158**:65, 1942.

The manifold nervous complications accompanying malaria in childhood have not yet been systematically explored. There is no real age disposition for these complications. In endemic regions they are probably more prevalent in children than in adults; in more sporadic districts they are just as numerous in the one group as in the other. These complications are also found in moderate climates and are not confined to tropical or subtropical countries.

From his own experience the author suggests the following classification for complications in the nervous system in malaria:

A. Coma—Prodromal Stage

1. Cephalalgic form (excluding headache)

B. Coma

2. Coma with creeping commencement
3. Foudroyantes coma (apparent "sun stroke")
4. Meningitic form
6. Epileptic form with epilepsy-like beginning and transition to coma

C. Lesions with More or Less Subacute Progress

7. Neuritic form
8. Hemiplegic form
9. Neuropathic form
10. Psychosis

In cases of malarial coma, especially in the prodromal stage, there was as a secondary symptom a larger increase in the sugar content of the cerebrospinal fluid, which was independent of the blood sugar. This may be considered as the manifestation of a severe disturbance of barrier between the blood and the cerebrospinal fluid.

AUTHOR'S SUMMARY.

Chronic Infectious Diseases

POSSIBLE SIGNIFICANT ERRORS IN ROUTINE TUBERCULIN TESTS. NORMAN ROSENBERG and ARTHUR ALLEN, J. Lab. & Clin. Med. **26**:1652 (July) 1941.

The authors discuss the possible errors in the use of old tuberculin as a testing material. The errors resulting in volume of seepage by the use of the single syringe method are discussed. In place of the so-called single syringe method for dilution, they suggest a multiple pipet method. This technic is described.

GARD, Galveston, Texas.

WELTMANN'S COAGULATION REACTION IN THE SERUM IN PULMONARY AND IN EXTRAPULMONARY TUBERCULOSIS. GEORGE ADLER, Ann. pædiat. **156**:220, 1941.

Two hundred and eighty-six persons with pulmonary or extrapulmonary tuberculosis were tested with Weltmann's serum reaction. This method proved

to be useful. The zone of coagulation in the succession of diminishing concentrations of calcium chloride is called the "band of coagulation" (*Koagulationsband*). Of 203 patients suffering from active intrathoracic tuberculosis, only 17 had a normal and only 6 a broadened band of coagulation. An extremely short band of coagulation indicated exudative and caseous forms of tuberculosis of the lungs. Early infiltrations and caverns caused a shift of the band of coagulation to the left during the acute phase, while in the healing phase a more normal band of coagulation was found. In cases of chronic, fibrotic tuberculosis of the lungs the band of coagulation was rarely shortened, usually normal. The hematogenic forms of tuberculosis of the lungs had a less pronounced shortening of the band of coagulation, or nearly normal conditions. In cases of tuberculosis of the hilus the band of coagulation was generally shortened. The band of coagulation was always shortened in 10 cases of tuberculosis of the bones and joints and also in 7 cases of urogenital tuberculosis, while the reaction was normal in 2 of 7 cases of lymphoglandular tuberculosis, in 1 of 7 cases of tuberculous peritonitis and in 2 of 6 cases of tuberculosis of the eyes. In cases of abscess of the lungs, bronchiectasis, gravidity and neurofibromatosis the band of coagulation was shortened. The Weltmann reaction was helpful in the observation of development and the therapeutic control of the above-mentioned diseases. The reaction is of value as an addition to the determination of the sedimentation rate of erythrocytes and to hematologic determinations. In several cases the Weltmann reaction was superior to those methods.

AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

THROMBOCYTOPEN: A CONFIRMATORY REPORT. HUGH ROSE JR. and L. BRYCE BOYER, J. Clin. Investigation **20**:81 (Jan.) 1941.

Data are presented confirming the work of Troland and Lee, who found a platelet-reducing substance in the spleens of patients with idiopathic thrombopenic purpura. In rabbits inoculated with acetone-extracted material from the spleens of 2 patients with thrombopenia, the platelets dropped in number, whereas in rabbits inoculated with control extracts from other spleens there was no appreciable drop.

GUEST, Cincinnati.

THE EFFECTS OF THE PATENT DUCTUS ARTERIOSUS ON THE CIRCULATION. EUGENE C. EPPINGER, C. SIDNEY BURWELL and ROBERT E. GROSS, J. Clin. Investigation **20**:127 (March) 1941.

Studies of the circulation made on 6 patients, from 6 to 26 years of age, before and after surgical closure of an uncomplicated patent ductus arteriosus show that: (1) When the ductus arteriosus is open the blood flow is from the aorta to the pulmonary artery; (2) there is no flow of blood from the pulmonary artery to the aorta. Therefore, these patients do not have arterial unsaturation and are not cyanotic. (3) The volume of blood flowing from the aorta to the pulmonary artery varied from 4 to 19 liters per minute, which is 45 to 75 per cent of all the blood pumped into the aorta by the left ventricle. These flows occurred in patients with a large ductus and under temporary conditions which are known to elevate the output of the heart. (4) The left ventricle expelled from two to four times the volume of blood expelled by the right ventricle in a given period of time. (5) Adjustment of the circulation to the patent ductus may be made by an increase in the output of the left ventricle. If this is not sufficient to compensate completely for the leak through the ductus, there may be, in addition, a diminution of the blood flow to the periphery.

Comparable studies on dogs with an artificial aorta-pulmonary artery fistula showed similar circulatory adjustments.

GUEST, Cincinnati.

A Simple Modification of Weltmann's Coagulation Reaction. David H. Kling, J. Lab. & Clin. Med. **26**:1795 (Aug.) 1941.

The original serum coagulation reaction described by Weltmann involved the use of ten test tubes. This required the pipetting out of varying amounts of solution and made the technic rather cumbersome to be used as a routine procedure. This author has devised a method by which one tube is used, and he also gives a conversion table for the use of his method. He also feels that the method which he describes is more accurate than the other simplified technics which have been introduced in the past.

Gard, Galveston, Texas.

The Measurement of Cell Volume of Blood by the Evans Blue Dye Method. Alfred T. Shohl and Thomas H. Hunter, J. Lab. & Clin. Med. **26**:1829 (Aug.) 1941.

A colorimetric method for the determination of cell volume is described in this paper. This method is offered primarily as a standard of reference rather than as a clinical method, although the authors feel it could be used as a clinical method. The procedure is as follows: A known amount of blood is mixed with a known amount of dye (the dye in this case is Evans blue, also referred to as T-1824). Then the concentration of the dye in the plasma is determined with a photoelectric colorimeter. Since the dye is contained entirely within the plasma, the volume of the plasma is determined by this measurement and the relative amount of plasma in whole blood is calculated as a percentage; the cell volume is obtained by difference. It is felt by the authors that the error in this method is less than 1 per cent.

Gard, Galveston, Texas.

Plasma Albumin, Globulin, and Fibrinogen in Healthy Individuals from Birth to Adult Life. Robert M. Hill and Virginia Trevorrow, J. Lab. & Clin. Med. **26**:1838 (Aug.) 1941.

Hill and Trevorrow present a simple but accurate modification of the existing micro-Kjeldahl procedure. With methods described in this paper a complete analysis of total nitrogen, nonprotein nitrogen, fibrinogen, albumin plus nonprotein nitrogen and globulin plus fibrinogen may be done in duplicate on as small an amount of plasma as 0.8 cc. This method, which they feel is accurate enough for usual use, is very adaptable to institutions interested in methods of microanalysis.

Gard, Galveston, Texas.

A New Objective Circulation Time (Fluorescein Method). David B. Fishbach, J. Lab. & Clin. Med. **26**:1966 (Sept.) 1941.

To date the methods for estimating the speed of circulating blood have all been subjective. After injection of some material into the antecubital vein of the arm the patient states when he tastes something bitter, burning, etc. Such materials as sodium dehydrocholate, saccharin, calcium gluconate and magnesium sulfate have been used for these methods. Such methods cannot be used for small children or unconscious adults.

The new method uses a fluorescent substance, the color of which can be noted by use of ultraviolet rays with a Wood filter. Of the various dyes tried fluorescein gave the best color reaction, the next best being acriflavine. After a 10 per cent solution of sodium fluorescein in distilled water had been tried on rabbits, it was tried on human subjects, no toxic reactions being noted. The circulation time from the antecubital vein to the eye with this method was around twelve seconds.

(This method has the disadvantage that it requires a darkened room; this might have some influence so far as results on children are concerned.)

Gard, Galveston, Texas.

A Micromethod for the Weltmann Reaction. Paul B. Szanto and Emanuel Oxman, J. Lab. & Clin. Med. **27**:94 (Oct) 1941.

The author describes a micromethod for the Weltmann reaction. So little blood is needed that the necessary amount of serum may be obtained from a puncture of a finger or an ear, which removes the necessity of a venipuncture. For this reason this method is thought to be of value in the examination of children, because it can be done daily without repeated discomfort to the patient.

Gard, Galveston, Texas.

Athletic Activity at Puberty, with Special Reference to the Cardiac and Tuberculous Patient. Stanley Gibson, J. Pediat. **19**:382 (Sept.) 1941.

The athletic activity of the child at puberty depends on various factors. One must consider his athletic program in relation to his social activities, the amount of rest he obtains, his nutritional status, his habits and his physical build. The slender, narrow-chested, poorly muscled child will not be able to stand the wear and tear of athletic competition. There is a large group of children who suffer from neurocirculatory asthenia in the adolescent period, and these children deserve attention and may readily be rehabilitated. The child with congenital cardiac disease will limit his own activities, for he is well aware of his physical limitations. The child with rheumatic heart disease is more difficult to treat. The primary factor in treating the rheumatic adolescent is the determination of the presence or absence of rheumatic activity. In the presence of rheumatic activity all physical activity must be abolished. When rheumatic activity has subsided, even in the presence of valvular damage and some degree of cardiac enlargement a rigid regimen is not justified. A way of life which is temperate and which includes as much activity as can be undertaken without undue fatigue should be recommended. The tuberculous adolescent should be treated in the same way as the adolescent with rheumatism; he must have complete rest in the presence of any tuberculous activity. When the activity has ceased, physical exertion may be resumed.

Rauh, Cincinnati.

Congenital Heart Disease and the Electrocardiogram. George Eisenberg and Stanley Gibson, J. Pediat. **19**:452 (Oct.) 1941.

The electrocardiogram may be of valuable aid in the study of congenital heart disease. In some types of congenital heart disease, such as patent ductus arteriosus and interventricular septal defect, the tracings are normal. When an abnormality in the tracing is observed the presence of associated lesions must be suspected. The electrocardiogram will reveal heart block and congenital dextrocardia. The more severe the congenital heart condition is the more likely are changes to be found. The group of cyanotic conditions will give the most marked changes, the most characteristic being bizarre, widely diphasic QRS complexes and sharply pointed, high P waves in one or more leads.

Rauh, Cincinnati.

Secondary Anemias. F. Tecilazic, Med. ital. **21**:517 (Dec.) 1940.

The author describes the various forms of secondary anemia and then describes the treatment. Of interest is the hemolytic anemia caused by favism. The author considers favism as due to an anaphylactic shock in persons sensitized to the pollen of the fava bean. The disease can occur in persons who have inhaled the pollen or in breast-fed infants whose mothers have eaten the fava bean. The anemia occurs during the attack. The principal symptoms are vomiting, diarrhea, profound asthenia and sometimes loss of consciousness. In a few hours there are a reduction in the number of red blood cells and an icteric coloration of the skin. Hemoglobinuria and hematuria may occur. The liver and spleen are enlarged and painful. The attack lasts from a few hours to two or three days. Epinephrine hydrochloride is used in treatment.

Martoccio, Utica, N. Y.

VALUES OF PLASMA PHOSPHATASE AND BLOOD PHOSPHORUS IN HEALTHY CHILDREN BORN AT TERM AND IN PREMATURE CHILDREN. EINAR JOSEFSSON, Ann. pædiat. **157**:193, 1941.

Josefsson reports statistically calculated normal values for the contents of plasma phosphatase and blood phosphorus in healthy children up to the age of 2 years. The same values in the blood of premature infants are also discussed briefly. The determinations were carried out according to micromethods published previously in "Revue Française de Pédiatrie" (by blood phosphorus is meant the phosphate content of whole blood). FROM THE AUTHOR'S SUMMARY.

CURE OF CONGENITAL APLASTIC ANEMIA (BENJAMIN TYPE). MARGRIT ESSER, Ann. pædiat. **157**:366, 1941.

In a case of congenital aplastic anemia (Benjamin type) the disease was successfully cured by injecting blood from the umbilical cord. Formerly this illness proved fatal in all cases. The cure must be attributed to the injection and cannot be regarded as spontaneous; the reasons are given in the article.

AUTHOR'S SUMMARY.

PATHOGENESIS OF COOLEY'S ANEMIA. E. FREUDENBERG and MARGRIT ESSER, Ann. pædiat. **158**:128, 1942.

The authors report 2 cases of Cooley's anemia in brothers living in the German part of Switzerland. Intermixture of Italian blood is excluded.

A strict racial limitation is no more valid for Cooley's anemia than for other forms of mutation anemia. So far, 10 patients with this type of anemia which do not belong to Mediterranean races have been described. The name Mediterranean anemia is not justified.

There are forms of Cooley's anemia with mild courses, as Cooley himself supposed. The authors' observations form a contribution thereto.

Infectious conditions contribute to the manifestation of the disposition to Cooley's anemia. Especially favorable is the appearance of erythroblasts in the blood.

In the cases reported coproporphyrin in largely increased amount was found in the feces and in the bile from the urine. In both cases an increase of protoporphyrin in the erythrocytes was probable. In the marrow in both cases numerous red fluorescent erythroblasts were present, which points to the presence of porphyrin in the same.

The disturbance of the porphyrin metabolism in Cooley's anemia is of great importance.

AUTHORS' SUMMARY.

Diseases of Nose, Throat and Ear

A RADIOLOGIC STUDY OF MASTOIDS IN CHILDREN. L. A. GAGNIER JR., Canad. M. A. J. **45**:312 (Oct.) 1941.

The roentgenologic study of the mastoid of a child from birth to 5 years of age presents a certain difficulty of interpretation and is specially limited to the antral and periantral region.

However, during this period the examination is of value. MOORE, Omaha.

DEAFNESS IN CHILDREN. EDMUND PRINCE FOWLER, New York State J. Med. **41**:1543 (Aug. 1) 1941.

In testing 1,200,000 public school children in the city of New York hearing losses of 9 decibels or more from "speech hearing" were found in 4 per cent.

Since the outstanding preventive measure is intelligent observation in testing, it is urged that pediatricians examine carefully both newborn and older children for diseases of the ear. Frequent examination of the ears is important, and the ears of every child should be audiometrically tested on entering school and at six to twelve month intervals if hearing losses are detected. Politzerization and catheterization are much abused in youth and in later age. Use of the catheter is practically never indicated in infancy and childhood. Fowler does not favor early incision of the drum membrane unless the inflammation has become purulent. Repeated incisions of the drum are not advised, and the use of sulfanilamide and other chemotherapeutic agents in cases of uncomplicated acute and chronic otitis media is not favored. Repeated removal of nasopharyngeal lymphoid hypertrophies may do harm by production of scar tissue. "Avoid meddlesome surgery and meddlesome medicine. Every patient is a law unto himself." Mumps in children over 12 years of age causes involvement of the ears and deafness more often than is realized. No one knows why mumps causes deafness unless it is by an associated meningitis or meningoencephalitis involving the eighth nerve. Syphilis is exaggerated as a cause of deafness. The arsenicals used in its treatment may harm the hearing more than does the disease. "The most satisfactory treatment will always be preventive. It is most difficult to enforce." AIKMAN, Rochester, N. Y.

INDICATIONS FOR OPERATION ON THE EAR IN INFANCY. H. FLESCH, Ann. pædiat. **156**:348, 1941.

There is no longer any doubt that occult mastoiditis occurs more frequently in early infancy than was formerly supposed. When protracted irregular fluctuations of temperature have been noted in otitis media and the infant has lost weight in spite of careful nutrition, blood transfusions, etc., Flesch considers antrotomy to be indicated, after an adequate period of waiting, provided no symptoms of other complications have been observed. A precise term for delay cannot be fixed, as this depends on the amount of weight lost, the general clinical picture, etc. The author's treatment was successful in most cases. When inflammation of the middle ear is complicated by pneumonia, the latter disease should be cured first. Only in exceptional cases is it advisable to operate before. If the ear is afflicted in cases of toxicosis, paracentesis should be performed. Antrotomy should be resorted to only after every other treatment has failed. If one cannot find any alteration in the middle ear, the patient must not be operated on.

In cases within the author's experience in which the condition would otherwise have proved lethal cures have certainly been attained by antrotomy. But whether the operation appreciably reduces the high mortality of grave toxicosis is of course questionable.

AUTHOR'S SUMMARY.

STATISTICS ON ETIOLOGIC EXAMINATIONS CONDUCTED AT THE COUNTY SCHOOL FOR THE DEAF IN MUNICH. E. EMMERIG, Monatschr. f. Ohrenh. **74**:425 (Sept.) 1940.

With the law purporting to prevent inheritance of diseases or disease tendencies (*Erbkranke*) in mind, the students of a school for deaf children were examined and the statistical results evaluated. Of 237 children examined, deafness was inherited (the author says "perhaps") in 30 per cent, congenitally acquired (without apparent reason) in 27 per cent and acquired in 35.4 per cent and in 7.6 per cent it was of uncertain origin. This is interpreted as indicating a decrease in acquired deaf-mutism since the beginning of the century. On the basis of a study of ascendants in cases of inherited deafness, indirect transmission seems to prevail. An interesting sidelight is revealed, namely, that in families with deaf-mutism the average number of children is twice that in normal families (5 : 2.35) and that twin births are more frequent among these families. Only 18 per cent of the children were totally deaf, while 43.3 per cent had sufficient hearing left to enable them to learn by hearing rather than by lip reading or other methods. Separation of these two groups for teaching purposes seems advisable. Langen-

beck's rule of symmetric defects as an indication of inherited deafness should not be overestimated, inasmuch as the sign was not present in 21 per cent of children with inherited deafness who were examined. Several tables support the author's conclusions. In cases of the acquired form of deafness the etiologic factors given, in order of importance, are cerebral disease, disease of the ear, measles, trauma, forceps delivery, syphilis, whooping cough, diphtheria and grip. Many of the patients had sisters or brothers who were hard of hearing. In very few cases was deafness due to consanguinity. LEDERER, Chicago [ARCH. OTOLARYNG.].

PATHOLOGIC ASPECTS OF MASTOIDITIS. T. NISHIHATA, Monatschr. f. Ohrenh. **75**:31 (Jan.) 1941.

The author "rediscovers" mastoiditis. In 5 patients with acute otitis media who were subjected to operation on the second to the fifth day of the attacks he found that all the mastoid cells had signs of inflammation and suppuration. In 9 patients on whom operation was performed eleven to forty-three days after the onset of the otitis only partial involvement of the mastoid cells was present (but no mention is made as to whether surgical intervention was indicated). The author believes that the extension of the inflammatory process follows Stenger's route of invasion. The antrum may be free of involvement while cells of the posterior wall of the auditory canal and the *Schwellenzellen* may show pathologic changes, so that direct extension from the tympanic cavity may be suspected. Histologic studies are discussed (but not shown) to support the contention that there exists a latent stage between otitis media and mastoiditis and that a special nomenclature should be applied, such as the "latent stage of mastoiditis" or the "mastoid cells form of otitis media." Portmann's empyema of the mastoid may be an equivalent, but while Portmann described condensing osteitis, followed later by a ramifying osteitis throughout the mastoid process, the author believes that much greater changes are present within the cells of the route of extension. Therefore, the deeper cells are inflamed much earlier than was previously believed, and destruction of bone is present earlier than in the surrounding cells. These cells, meanwhile, evidence new bone formation. The observations are essentially the same as Portmann's, but the explanation differs in the main in the fact that the deep cells are affected earlier. LEDERER, Chicago [ARCH. OTOLARYNG.].

DEAF-MUTISM. E. URBANTSCHITSCH, Monatschr. f. Ohrenh. **75**:36 (Jan.) 1941.

The author discusses the premise of replacing the newly introduced nomenclature applied to deaf-mutes by the proper expression, which has been used without any confusion for some time. Deaf-mutes are persons who have lost their hearing before the development of speech faculties and who therefore do not learn to speak through the natural channels of hearing. Speech thus acquired is not normal. Urbantschitsch, therefore, makes a plea for the return of the more universally known and more descriptive terms "deaf-mute" and "deaf-mutism."

LEDERER, Chicago [ARCH. OTOLARYNG.].

TONSILLECTOMY IN CASES OF PERITONSILLAR ABSCESS. W. HAARDT, Monatschr. f. Ohrenh. **75**:93 (Feb.) 1941.

In 100 cases of peritonsillar abscess, five types of tonsillectomy were used: unilateral, with the patient under general anesthesia; bilateral, with the patient under general anesthesia; unilateral, with the region under local anesthesia; bilateral, with the region under local anesthesia, and tonsillectomy during the "lukewarm" stage. Ninety-four of the patients recovered without any complications, 2 died "without death being attributable to surgery" and 4 recovered despite complications (sepsis). According to Haardt, a review of the literature reveals excellent results in thousands of cases. The best and simplest results are achieved with unilateral tonsillectomy with the patient under a light general anesthesia. In bilateral tonsillectomy the uninvolved side often bleeds more than the abscessed

side. In several cases in which the operation was performed with the region under local anesthesia, a slight increase in temperature was noted after operation.

In general it must be admitted that 87 to 99 per cent of all peritonsillar abscesses will heal either by spontaneous rupture or after incision. However, in cases of deep abscess, insufficient drainage, phlegmon, nephritis, sepsis and the like, "abscess tonsillectomy" should be performed, combined eventually with an external operation. Tonsillectomy in the "lukewarm stage," two to seven days after incision of the abscess, has given rise to septic conditions and therefore has been discontinued. A symptom which might be useful in diagnosing hidden abscess consists of provoking a retching reflex. Normally the tonsil and posterior pillar move toward the midline. This is lacking in the presence of an abscess. Seventy-four per cent of the abscesses were found near the upper pole, 17 per cent next to and back of the tonsil and 6 per cent (small abscesses) close to the inferior pole.

LEDERER, Chicago [ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura and Mediastinum

CUTANEOUS REACTIONS WITH SPECIFIC SOLUBLE SUBSTANCE IN INFANTS AND CHILDREN. RUBEN MEYER and BENJAMIN W. CAREY, J. Pediat. **19**:481 (Oct.) 1941.

Forty-two patients with typed pneumococcic pneumonia were studied with the Francis test. Of these, 9 were treated with sulfapyridine, 9 with sulfapyridine and serum, 12 with sulfathiazole and 12 with sulfathiazole and serum. In the Francis test polysaccharides derived from pneumococcus culture are injected intradermally. The polysaccharide is homologous in type with the pneumococcus causing the infection. One-tenth cubic centimeter is injected intradermally after the first dose of serum is given. A positive reaction, a wheal and erythema, indicates that sufficient serum has been administered. The positive reaction probably is due to a local union of antigen and antibody. When specific antipneumococcus serum was given intravenously, it was found that only one cutaneous test dose needed to be administered and that after the area of this injection showed a positive reaction serum therapy could be discontinued. By utilizing the Francis test, less serum was given with comparable therapeutic effects. The time of development and intensity of cutaneous reactions varied greatly when patients received only chemotherapy. On the other hand, patients who received serum had strong reactions which persisted throughout their stay in the hospital.

RAUH, Cincinnati.

PSEUDOSYPHILITIC BRONCHOPNEUMONIA (PULMONARY INFILTRATIONS WITH POSITIVE WASSERMANN REACTIONS). ILSE BENEDIKT, Ann. pædiat. **157**:340, 1941.

After a review of the literature, especially the works of Fanconi and Hegglin, 7 cases of pseudosyphilitic bronchopneumonia in children of school age and 1 not quite definite case of syphilitic pneumonia are reported. The cases are classified as follows:

1. Certain: Either the Wassermann reaction and the flocculation reaction or only the Wassermann reaction were positive several times.

2. Uncertain: The Wassermann reaction alone or the flocculation reaction was weakly positive once.

3. Unclear: Antisyphilitic treatment was given because of the clinical and anamnestic data presented in the case.

The clinical symptoms and the three cardinal ones described by Fanconi for pseudosyphilitic pneumonia are stressed:

1. The subacute, sometimes focal, often more hilar bronchopneumonia, with little or no increase in temperature: Roentgen rays revealed the changes on the

hilus mentioned by Fanconi and also the infiltration described by Hegglin. In this case participation of the bronchial glands was less pronounced than in the 4 first cases of Fanconi.

2. The generally enfeebled child: Fanconi's observations were here fully confirmed. The character of the condition is the opposite of the clinical symptoms in adults (Hegglin); the condition has been observed in strong young men.

3. The positive, spontaneously disappearing syphilitic reactions: The boundary between tuberculosis and syphilis must be drawn. Concerning the latter, it is of the greatest importance to note the spontaneous disappearing of the serologic reaction, as otherwise it is impossible to decide whether the negative reactions are spontaneous or the consequence of the antisyphilitic treatment.

AUTHOR'S SUMMARY.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE RELATION OF NUTRITION TO GASTRIC FUNCTION: IV. THE EFFECT OF VITAMAN A DEFICIENCY. HELEN M. DYER and JOSEPH H. ROE, Am. J. Digest. Dis. **8**:333 (Sept.) 1941.

The same procedure was followed in this experiment, the subjects being albino rats.

The mortality was enormous; only 27 of 155 rats placed on the vitamin A–deficient diets during the course of the experiment survived through gastric analysis.

Acute deficiency of vitamin A in young rats had no effect on the ability of the gastric cells to secrete acid or mucin.

Chronic deficiency of vitamin A of alternating mildness and severity maintained for five to seven months in young adult rats had no significant effect on the secretory activity of the gastric mucosa.

The livers of the control rats (vitamin A–sufficient) maintained for five to seven months on the basal diet supplemented with 4 per cent cod liver oil contained an average of 9,088 U. S. P. units of vitamin A per gram of liver, while the livers of the animals chronically deficient in vitamin A had an average content of 5.6 units per gram.

MORRISON, Savannah, Ga.

HEREDITARY HEMORRHAGIC TELANGIECTASIA WITH GASTRO-INTESTINAL BLEEDING. DONALD E. GRIGGS and MARSHALL Q. BAKER, Am. J. Digest. Dis. **8**:344 (Sept.) 1941.

Three cases of multiple familial hemorrhagic telangiectasia with hemorrhage from the gastrointestinal tract are reported. The source of the bleeding is believed to have been telangiectatic areas in the stomach or elsewhere in the intestinal tract. In 1 of the 3 patients on gastroscopic examination the visualized gastric mucosa appeared normal. Repeated epistaxis occurred in all cases. The importance of bearing this condition in mind in the differential diagnosis of hematemesis and melena when the cause of the bleeding is obscure is emphasized.

All of the patients were adults, aged 39, 50 and 69 years. There were several instances of death from spontaneous hemorrhage elicited in the family histories. All 3 patients complained of some abdominal pain or distress at times, especially during periods of active bleeding.

MORRISON, Savannah, Ga.

THE RELATION OF THE NASOPHARYNGITIS TO ULCERATIVE COLITIS. S. WEISS, A. SLANGER and S. GOODFRIEND, J. Lab. & Clin. Med. **26**:1925 (Sept.) 1941.

The authors report the case of a 13 year old boy with ulcerative colitis. This lad was treated with vaccines prepared from organisms which were present simultaneously in the nose, throat and rectosigmoid. After his condition had become worse in the hospital and he had reached a low weight of 84 pounds (38.1 Kg.),

the boy began to improve. Vaccine therapy was given both in the hospital and at home. His first proctosigmoidoscopy, on Jan. 4, 1938 revealed: "Entire rectosigmoid mucosa showed marked redness with some false membrane formation." There were numerous ulcerated areas. On March 20 a check-up examination showed a normal-appearing mucosa throughout. By December 3 this boy's weight had increased to 137.5 pounds (62.4 Kg.), and he was having one normally formed bowel movement a day.

GARD, Galveston, Texas.

LABORATORY AIDS IN THE DIAGNOSIS AND CONTROL OF ENTERIC DISEASE. ALBERT H. HARRIS, New York State J. Med. **41**:1444 (July 15) 1941.

Dr. Harris is from the division of laboratories and research, New York State Department of Health. In the state of New York the major part of the laboratory work necessary for the diagnosis and control of enteric diseases is done by local approved laboratories collaborating with the state laboratory.

AIKMAN, Rochester, N. Y.

THE TREATMENT OF FOOD-BORNE DISEASES OF THE GASTROINTESTINAL TRACT. Z. BERCOVITZ, New York State J. Med. **41**:1450 (July 15) 1941.

This study, the fourth of a series of articles in a symposium on food-borne diseases of the gastrointestinal tract, lists the various conditions and outlines their treatment.

Chiniofon in enteric-coated tablets (anayodin) is recommended as the drug of choice against both acute and chronic amebic dysentery. There may be some irritation from the drug, which contains 25 per cent iodine, when acute involvement of the intestine is present.

AIKMAN, Rochester, N. Y.

DUODENAL ATRESIA WITH A CASE REPORT OF A SUCCESSFUL GASTRO-ENTEROSTOMY. P. M. KELLY, Brit. J. Surg. **29**: 245 (Oct.) 1941.

It is estimated that duodenal atresia occurs once in 20,000 births. The author cites five points in diagnosis: (1) persistent vomiting from birth; (2) vomitus usually containing bile and sometimes pure or altered blood and vomiting usually projectile; (3) fulness in the epigastrium with or without peristaltic waves from left to right; (4) constipation from birth, though meconium may be passed; (5) typical picture in roentgenograms taken after a barium sulfate meal. The author has collected only 10 cases in which operation was successfully performed. A case is described in a 3 day old infant operated on by the author, in which a successful gastroenterostomy was performed. Two months after operation the child was doing well.

KEITH, Toronto, Canada.

CONGENITAL ATRESIA OF THE BILE DUCTS. GUSTAVO CARDELLE, ARGELIO GARCIA, JUAN JIMENEZ and FERNANDO SALA, Arch. de med. inf. **10**:191 (Oct.) 1941.

Three cases of congenital atresia of the bile ducts are reported in which there were atrophy of the vesicular and extrahepatic ducts and no cystic or extrahepatic ducts. Complete autopsy observations and photographs are shown. All of the patients died before they were 5 months of age.

SANFORD, Chicago.

ENTEROCOLITIS FROM THE FLEXNER BACILLUS CURED WITH SULFAGUANIDINE. VICTOR SANTAMARINA and D. SOSA BENS, Arch. de med. in. **10**:213 (Oct.) 1941.

The authors report a case of enterocolitis caused by the Flexner bacillus in a 14 month old child. Recovery followed treatment with sulfaguanidine.

SANFORD, Chicago.

CHOLASCOS IN CHILDHOOD. EDUARD MELCHIOR, Ann. pædiat. **156**:364, 1941.

Following his own observations of cases the author described the clinical picture of cholascos, an exudation of bile into the peritoneum. The prognosis is bad if there is no surgical intervention. The author discusses the conditions for the development of a temporarily stationary biliary exudate in the abdomen after injury; cholate poisoning plays an important part in these conditions. The possibilities for the formation of a nontraumatic cholascos are discussed.

FROM THE AUTHOR'S SUMMARY.

CLINICAL USE OF ADRENAL CORTEX EXTRACT IN CELIAC DISEASE. MATHILDE KRAFT, Ann. pædiat. **158**:1, 1942.

The clinical use of an adrenal cortex extract in celiac disease was tested in 6 cases. According to the author's experience, this extract (percorten) had no effect on the fat resorption and the water content of the feces in celiac disease; on the other hand, the well known increase in water retention was definitely observed. Doses of 5 to 10 mg. per day may cause the development of edema. After acute loss of weight this effect of adrenal cortex extract may be utilized. In no case, however, can such therapy take the place of dietetic treatment. In 2 of the 6 cases of celiac disease there was a decrease in or absence of pancreatic diastase. The therapeutic administration of preparations of pancreas proved useful.

AUTHOR'S SUMMARY.

MONOCYTIC AND MYELOID-LEUKEMOID REACTION IN SEVERE FIBRINOUS-NECROTIC STOMATITIS OF A CHILD. E. KRUEGER, Arch. f. Kinderh. **118**:113 (Dec. 19) 1939.

An infant 18 months of age became ill with the symptoms of a febrile infection: rhinitis, conjunctivitis, otitis media and a peculiar fibrinous necrotic stomatitis. At the climax of the disease practically no granulocytes were found in the blood smear; the white blood cell count was in normal range, with an exceedingly high number of monocytes, including many immature forms. The stomatitis cleared up with a "recovery phase" of leukemic-myeloid character. The leukocyte count rose to 29,000, with formation of an increased number of pathologic cell forms; the number of monocytes decreased progressively. At the time the infant recovered, a normal blood picture was found. In this case the monocytic or monocytic-leukemoid reaction shifted into a myeloid-leukemoid reaction. The myeloid-leukemoid reaction may be a symptom of the subsiding infection or may be caused by the process of repair. The reported case cannot be classified as an instance of typical agranulocytosis nor of infectious mononucleosis; the spleen and the lymph nodes were not enlarged, and diphtheroid tonsillitis was also missing.

ARON, Chicago.

CONGENITAL UMBILICAL FISTULA OR SINUS DUE TO PERSISTENT OMPHALOMESENTERIC DUCT. Y. K. WU and S. T. YU, Chinese M. J. **60**:264 (Sept.) 1941.

The authors state that this anomalous condition belonging to infancy or early childhood not only is of rare occurrence but is neglected in most medical publications. Four examples, however, have been seen in the surgical service in the last four years at the Peiping Union Medical College Hospital. Because it may not be so rare as supposed, the authors give a short report dealing with the cause, the therapy and clinical observations. All 4 of the patients were boys, which conforms to the tendency for the condition to occur in the male sex. The hospital observations began on the 4 children at the ages of 1 month, 6 months, 20 months and 3 years respectively. In the 3 on whom operation was performed the procedures were described; all made uncomplicated convalescences. Readers are referred to the article for the brief discussion of the embryologic background as well as the clinical picture and treatment.

NEFF, Kansas City, Mo.

the boy began to improve. Vaccine therapy was given both in the hospital and at home. His first proctosigmoidoscopy, on Jan. 4, 1938 revealed: "Entire rectosigmoid mucosa showed marked redness with some false membrane formation." There were numerous ulcerated areas. On March 20 a check-up examination showed a normal-appearing mucosa throughouf. By December 3 this boy's weight had increased to 137.5 pounds (62.4 Kg.), and he was having one normally formed bowel movement a day.

GARD, Galveston, Texas.

LABORATORY AIDS IN THE DIAGNOSIS AND CONTROL OF ENTERIC DISEASE. ALBERT H. HARRIS, New York State J. Med. **41**:1444 (July 15) 1941.

Dr. Harris is from the division of laboratories and research, New York State Department of Health. In the state of New York the major part of the laboratory work necessary for the diagnosis and control of enteric diseases is done by local approved laboratories collaborating with the state laboratory.

AIKMAN, Rochester, N. Y.

THE TREATMENT OF FOOD-BORNE DISEASES OF THE GASTROINTESTINAL TRACT. Z. BERCOVITZ, New York State J. Med. **41**:1450 (July 15) 1941.

This study, the fourth of a series of articles in a symposium on food-borne diseases of the gastrointestinal tract, lists the various conditions and outlines their treatment.

Chiniofon in enteric-coated tablets (anayodin) is recommended as the drug of choice against both acute and chronic amebic dysentery. There may be some irritation from the drug, which contains 25 per cent iodine, when acute involvement of the intestine is present.

AIKMAN, Rochester, N. Y.

DUODENAL ATRESIA WITH A CASE REPORT OF A SUCCESSFUL GASTRO-ENTEROSTOMY. P. M. KELLY, Brit. J. Surg. **29**: 245 (Oct.) 1941.

It is estimated that duodenal atresia occurs once in 20,000 births. The author cites five points in diagnosis: (1) persistent vomiting from birth; (2) vomitus usually containing bile and sometimes pure or altered blood and vomiting usually projectile; (3) fulness in the epigastrium with or without peristaltic waves from left to right; (4) constipation from birth, though meconium may be passed; (5) typical picture in roentgenograms taken after a barium sulfate meal. The author has collected only 10 cases in which operation was successfully performed. A case is described in a 3 day old infant operated on by the author, in which a successful gastroenterostomy was performed. Two months after operation the child was doing well.

KEITH, Toronto, Canada.

CONGENITAL ATRESIA OF THE BILE DUCTS. GUSTAVO CARDELLE, ARGELIO GARCIA, JUAN JIMENEZ and FERNANDO SALA, Arch. de med. inf. **10**:191 (Oct.) 1941.

Three cases of congenital atresia of the bile ducts are reported in which there were atrophy of the vesicular and extrahepatic ducts and no cystic or extrahepatic ducts. Complete autopsy observations and photographs are shown. All of the patients died before they were 5 months of age.

SANFORD, Chicago.

ENTEROCOLITIS FROM THE FLEXNER BACILLUS CURED WITH SULFAGUANIDINE. VICTOR SANTAMARINA and D. SOSA BENS, Arch. de med. in. **10**:213 (Oct.) 1941.

The authors report a case of enterocolitis caused by the Flexner bacillus in a 14 month old child. Recovery followed treatment with sulfaguanidine.

SANFORD, Chicago.

CHOLASCOS IN CHILDHOOD. EDUARD MELCHIOR, Ann. pædiat. **156**:364, 1941.

Following his own observations of cases the author described the clinical picture of cholascos, an exudation of bile into the peritoneum. The prognosis is bad if there is no surgical intervention. The author discusses the conditions for the development of a temporarily stationary biliary exudate in the abdomen after injury; cholate poisoning plays an important part in these conditions. The possibilities for the formation of a nontraumatic cholascos are discussed.

FROM THE AUTHOR'S SUMMARY.

CLINICAL USE OF ADRENAL CORTEX EXTRACT IN CELIAC DISEASE. MATHILDE KRAFT, Ann. pædiat. **158**:1, 1942.

The clinical use of an adrenal cortex extract in celiac disease was tested in 6 cases. According to the author's experience, this extract (percorten) had no effect on the fat resorption and the water content of the feces in celiac disease; on the other hand, the well known increase in water retention was definitely observed. Doses of 5 to 10 mg. per day may cause the development of edema. After acute loss of weight this effect of adrenal cortex extract may be utilized. In no case, however, can such therapy take the place of dietetic treatment. In 2 of the 6 cases of celiac disease there was a decrease in or absence of pancreatic diastase. The therapeutic administration of preparations of pancreas proved useful.

AUTHOR'S SUMMARY.

MONOCYTIC AND MYELOID-LEUKEMOID REACTION IN SEVERE FIBRINOUS-NECROTIC STOMATITIS OF A CHILD. E. KRUEGER, Arch. f. Kinderh. **118**:113 (Dec. 19) 1939.

An infant 18 months of age became ill with the symptoms of a febrile infection: rhinitis, conjunctivitis, otitis media and a peculiar fibrinous necrotic stomatitis. At the climax of the disease practically no granulocytes were found in the blood smear; the white blood cell count was in normal range, with an exceedingly high number of monocytes, including many immature forms. The stomatitis cleared up with a "recovery phase" of leukemic-myeloid character. The leukocyte count rose to 29,000, with formation of an increased number of pathologic cell forms; the number of monocytes decreased progressively. At the time the infant recovered, a normal blood picture was found. In this case the monocytic or monocytic-leukemoid reaction shifted into a myeloid-leukemoid reaction. The myeloid-leukemoid reaction may be a symptom of the subsiding infection or may be caused by the process of repair. The reported case cannot be classified as an instance of typical agranulocytosis nor of infectious mononucleosis; the spleen and the lymph nodes were not enlarged, and diphtheroid tonsillitis was also missing.

ARON, Chicago.

CONGENITAL UMBILICAL FISTULA OR SINUS DUE TO PERSISTENT OMPHALOMESENTERIC DUCT. Y. K. WU and S. T. YU, Chinese M. J. **60**:264 (Sept.) 1941.

The authors state that this anomalous condition belonging to infancy or early childhood not only is of rare occurrence but is neglected in most medical publications. Four examples, however, have been seen in the surgical service in the last four years at the Peiping Union Medical College Hospital. Because it may not be so rare as supposed, the authors give a short report dealing with the cause, the therapy and clinical observations. All 4 of the patients were boys, which conforms to the tendency for the condition to occur in the male sex. The hospital observations began on the 4 children at the ages of 1 month, 6 months, 20 months and 3 years respectively. In the 3 on whom operation was performed the procedures were described; all made uncomplicated convalescences. Readers are referred to the article for the brief discussion of the embryologic background as well as the clinical picture and treatment.

NEFF, Kansas City, Mo.

Nervous Diseases

ENORMOUS MYELOMENINGOCELE WITH FATAL LEAKAGE. ARTHUR D. ECKER, New York State J. Med. **41**:1549 (Aug. 1) 1941.

The sac, which at birth was the size of a small grapefruit, grew gradually in size. When the patient was 1 year of age, when operative intervention was being contemplated, fluid began to leak from the sac, and 5,000 cc. was then aspirated. A firm bandage was applied to prevent cerebellomedullary herniation. The child died, and at autopsy a tonguelike projection of the left cerebellar lobe into the foramen magnum and the upper part of the spinal canal was found. This downward prolongation of the cerebellum and medulla oblongata into the spinal canal has been described as the Arnold-Chiari malformation. This malformation is almost always found in children with myelomeningocele.

AIKMAN, Rochester, N. Y.

LYMPHOCYTIC CHORIOMENINGITIS: TWO HUMAN FATALITIES FOLLOWING AN UNUSUAL FEBRILE ILLNESS. J. E. SMADEL, R. H. GREEN, R. M. PALTAUF and T. A. GONZALES, Proc. Soc. Exper. Biol. & Med. **49**:683 (April) 1942.

Two men, laboratory workers, one of whom participated in the autopsy of the first, succumbed to acute febrile systemic illness of twelve and eighteen days' duration respectively. Study of the tissues of these subjects by injection into guinea pigs and mice disclosed the presence of the virus of lymphocytic choriomeningitis.

HANSEN, Minneapolis.

WERNICKE'S ENCEPHALOPATHY: THE CLINICAL FEATURES AND THEIR PROBABLE RELATIONSHIP TO VITAMIN B DEFICIENCY. A. C. P. CAMPBELL and W. RITCHIE RUSSELL, Quart. J. Med. **10**:41 (Jan.) 1941.

The authors reported 21 cases of Wernicke's encephalopathy in which the diagnosis was confirmed at autopsy. The pathologic changes in this disease, which Wernicke in 1881 described as an acute superior hemorrhagic polioencephalitis, consist of foci of vascular stasis and parenchymatous degeneration, occurring symmetrically in the corpora mamillaria and also, though not constantly, in other parts of the hypothalamus, the fornix, the midbrain, the posterior colliculi and the floor of the fourth ventricle; lesions are occasionally found elsewhere.

The encephalopathy occurred as a complication of chronic alcoholism, gastric carcinoma and other gastrointestinal disorders, pernicious anemia and vomiting of pregnancy and in association with certain infectious diseases.

Pathologic evidence of healing of the lesions occurred, and 2 cases were described in which there was probable recovery, in 1 in response to the administration of vitamin B_1.

The authors point out that the association of Wernicke's disease with alimentary disturbance and with polyneuritis strongly suggests that a vitamin deficiency is concerned in its production.

BRADFORD, Rochester, N. Y.

CAUSE OF EDEMA IN TETANY. E. FREUDENBERG, Ann pædiat. **158**:34, 1942.

Edema in infantile tetany is explained by increased permeability of the vessels in consequence of hypocalcemia. Experimental and clinical reasons are given. The special tendency toward generalized cramps in many forms of tetany (infantile tetany, tetany with pertussis and tetany with epilepsy in adults) is to be explained by an abnormal increase in water in the brain in consequence of hypocalcemic increase of permeability.

AUTHOR'S SUMMARY.

INTRACRANIAL ANEURYSM. HUGO KRAYENBÜHL, Schweiz. Arch. f. Neurol. u. Psychiat. **47**:155, 1941.

This contribution is based on a comprehensive review of the literature and the author's experience in 32 cases of intracranial aneurysm of the saccular type. In

a group of 11 cases in which the diagnosis was confirmed either by arteriographic examination with a colloidal suspension of thorium dioxide or by surgical exploration all the patients were alive. Their ages at the time of observation varied from 12 to 50 years. In 2 cases of infraclinoidal aneurysm of the internal carotid artery extracranial ligation of that vessel was done. Both patients were completely relieved of pain, and their ocular palsies were greatly improved. Clinical signs in the first case consisted of paralysis of the external rectus muscle on the affected side with slight exophthalmos and a minimal degree of corneal anesthesia. A large aneurysm was revealed in arteriograms. In the second case there were exophthalmos, atrophy of the optic nerve and almost complete ophthalmoplegia on the affected side with loss of sensation in areas innervated by the first and second divisions of the trigeminal nerve. Although arteriograms showed nothing abnormal aside from posterior displacement of the middle cerebral artery, a large aneurysm was discovered on surgical exploration. Roentgenologic examination in both cases revealed homolateral erosion of the sella turcica and neighboring structures.

In 2 additional cases of infraclinoidal aneurysm of the internal carotid artery, failure of vision was the chief complaint and perimetric study disclosed bitemporal hemianopia. Arteriographic examination gave negative results in both cases, and roentgenologic examination revealed expansion of the sella turcica with atrophy of the dorsum sellae in only 1 of them. In both instances, however, an intrasellar aneurysm was demonstrated on surgical exploration. In 1 of these cases the aneurysm remained in a collapsed state after its contents were aspirated, with resulting improvement of the bitemporal defect in the visual fields. Signs and symptoms of a progressive lesion of the optic chiasm were likewise noted in a case of supraclinoidal aneurysm of the left anterior cerebral artery. Arteriograms revealed a sac of huge dimensions, and eight days after ligation of the left common and internal carotid arteries there was considerable improvement in the right visual field.

Recurring subarachnoid hemorrhage was the indication for arteriographic examination and immediate ligation of the common and internal carotid arteries on the affected side in 2 other cases of supraclinoidal aneurysm. Although in serious condition at the time of operation, both patients recovered. The aneurysm arose from the anterior communicating artery at its junction with the right anterior cerebral artery in the 1 case and from the left anterior cerebral artery in the other. The oculomotor nerve and the first division of the trigeminal nerve were involved in the fourth and fifth cases of supraclinoidal aneurysm. In each of the last-mentioned cases the aneurysmal sac, as demonstrated in arteriograms, arose from the internal carotid artery at the origin of the posterior communicating artery. Ligation of the internal carotid artery in the 1 case and of the common and internal carotid arteries in the other was followed by marked improvement. No operative treatment was undertaken in a case of aneurysm of the posterior portion of the left posterior communicating artery with oculomotor palsy and recurring subarachnoid hemorrhage. Injection of a colloidal suspension of thorium dioxide into the left internal carotid artery gave negative arteriographic results, but the aneurysm was finally demonstrated by injection of the contrast medium into the right vertebral artery according to the method of Moniz. Moniz' method consists in injecting the medium into the subclavian artery after the vessel has been exposed and its distal end occluded.

In the eleventh case, that of a boy aged 15, hemiplegia had developed suddenly on the right side ten months previously, and the patient subsequently had jacksonian seizures. Arteriographic examination revealed dilatation of the left internal carotid artery at the level of the cavernous sinus but failed to show the left middle cerebral artery. A presumptive diagnosis of thrombosis of the left middle cerebral artery was confirmed on surgical exploration, which, in addition, disclosed a large thrombosed aneurysm of the same vessel. The aneurysm, which was of the congenital type and lay in the white matter of the left frontal lobe, was removed.

In the series of 7,452 autopsies studied, ruptured intracranial aneurysm was found to be the cause of death in 21 cases. The patients' ages ranged from 6 to

78 years. The sites of aneurysm were as follows: anterior cerebral artery, 6 cases; anterior communicating artery, 4 cases; middle cerebral artery, 4 cases; internal carotid artery, 4 cases; basilar artery, 2 cases, and a cerebellar artery, 1 case. Formation of aneurysm was due to arteriosclerosis in 2 cases, focal arteritis in 4 cases and arteritis of embolic origin (mycotic aneurysm) in 1 case. In 6 cases the ruptured aneurysm was of the congenital type, and in the remaining 8 cases the type was not stated. Of 20 cases in which a clinical history was available, the onset of symptoms was abrupt in 16 and gradual in 4. In 1 of the cases of aneurysm of the anterior communicating artery homonymous hemianopia was present. In only 1 of the 7,452 autopsies was note made of an intracranial aneurysm which had been obliterated by thrombosis and subsequent fibrosis.

Clinically, intracranial aneurysms are divided into the paralytic and the apoplectic type. Aneurysm of the internal carotid artery in its course through the cavernous sinus gives rise to a characteristic syndrome consisting of pain and sensory loss in the area of distribution of the cranial nerve and ocular palsies, oculomotor palsy being the most important. All three divisions of the trigeminal nerve are, in general, involved only when the aneurysm lies in the posterior portion of the cavernous sinus; involvement of the first and second divisions is characteristic of an aneurysm in the middle portion of the sinus, whereas involvement of the ophthalmic division alone suggests a more anterior location. The author's first 2 cases were somewhat unusual in that symptoms characteristic of the cavernous sinus syndrome came on gradually, rather than abruptly. The symptoms and signs of an intrasellar aneurysm may differ little from those due to an intrasellar neoplasm. Focal symptoms are much less frequent in cases of aneurysm of the anterior cerebral or the anterior communicating artery. Aneurysm of either the internal carotid or the posterior communicating artery at or near the junction of the two arteries is productive of a well defined clinical picture, consisting of oculomotor palsy and homolateral headache with pain in either the eye or the forehead. Aneurysm of the posterior cerebral artery at the origin of the posterior communicating artery is relatively rare. The symptoms of aneurysm of the middle cerebral artery are not especially characteristic. Bilateral involvement of the sixth cranial nerve when associated with subarachnoid hemorrhage is strongly suggestive of aneurysm of the basilar artery.

Two cases illustrative of the value of cerebral arteriography in differential diagnosis are reported. One was a case of arteriovenous aneurysm with recurring subarachnoid hemorrhage, while the other was one of cerebral glioma with an apoplectiform onset. Valuable though cerebral arteriography is in the diagnosis of intracranial aneurysm, it furnishes no information as to the possible risk of carotid ligation. In none of the author's cases was the contrast medium demonstrated in the opposite half of the circle of Willis, not even when it was injected into one internal carotid artery after the other had been ligated. Although manual compression of the carotid artery for periods of fifteen to twenty minutes on several successive days is a helpful test, it furnishes no positive assurance that the effects of carotid ligation will not be disastrous. In a few of Krayenbühl's cases severe homolateral headache persisted a few days after the procedure, and in 1 case Babinski's reflex could be demonstrated for a time on the opposite side. In 1 or 2 cases of arteriovenous aneurysm, carotid ligation was followed by hemiplegia and aphasia, both of which receded later. Contrary to a view previously expressed, Krayenbühl's experience would indicate that ligation of the internal carotid artery is beneficial even in cases of aneurysm lying distal to the circle of Willis.

DANIELS, Denver [ARCH. NEUROL. & PSYCHIAT.].

Psychology and Psychiatry

SEXUAL EDUCATION OF THE ADOLESCENT. GEORGE J. MOHR, J. Pediat. **19**:387 (Sept.) 1941.

Children should be fully oriented and informed about anatomic differences between the sexes and the normal functioning of all the bodily systems, including

the generative organs, before adolescence is reached. If the child understands this, he is unlikely to have any difficulty in frankly raising issues with parents or educators when puzzling or disturbing considerations arise and he accepts a rational discussion of practical issues relating to sexual interest or conduct with a minimum of resistance or anxiety. Parents are the persons best qualified to instruct their children in sexual matters. If the parents are unable to instruct them successfully, the physician, especially the pediatrician who has known the child throughout his life, is in a position of advantage to be helpful to parents and children in providing instruction and counsel in this field.

RAUH, Cincinnati.

Diseases of the Genitourinary Tract

THE TOXICITY OF ORALLY ADMINISTERED POTASSIUM SALTS IN RENAL INSUFFICIENCY. A. W. WINKLER, H. E. HOFF and P. K. SMITH, J. Clin. Investigation **20**:119 (March) 1941.

The general subject of the toxicity of potassium salts in renal insufficiency is discussed, and experiments are described showing that death from cardiac failure due to orally administered potassium could be produced in dogs whose ureters were tied. From observations on human subjects the authors conclude that poisoning from orally administered potassium is a distinct possibility when there is complete anuria from any cause but that so long as urine is being excreted the continued ability of the most severely damaged kidney to excrete potassium makes such poisoning difficult to bring about.

GUEST, Cincinnati.

MENSTRUAL ABNORMALITIES OF ADOLESCENCE. E. L. SEVRINGHAUS, J. Pediat. **19**:319 (Sept.) 1941.

The onset of the menarche in girls in the northern portion of the United States occurs on an average at about 14 years of age, with a spread from 12 to 15 years. Southern types do not mature earlier: If there is any deviation it is a tendency to slightly later maturity. Menstruation occurring before the age of 12 years may be considered precocious and after the age of 15 years may be considered delayed. If no evidence of pelvic disease or physical abnormality of the genitals is present, endocrine disorder must be considered the cause of the delay in onset of menstruation. In addition to amenorrhea the author believes oligomenorrhea and menorrhagia to be manifestations of hypogonadal and hypopituitary function. Sevringhaus believes tissue studies of the endometrium and vaginal mucosa should be done to establish a diagnosis of hypogonadal function. Treatment of patients with delayed adolescence, incomplete adolescence and other manifestations of hypogonadism should be with gonadotropic anterior pituitary materials, of which those on the market at present are far from satisfactory. In addition, extracts made from the serum of pregnant mares stimulate the ovary of the human female in the same way that the pituitary extract does. Chorionic gonadotropin, which has been widely used, has for its sole action a check on the ovaries during pregnancy, so that the ovaries shall not have a sequence of ovarian cycles maturing ova and forming fresh corpora lutea. This material does not stimulate the ovaries. Thyroid should be used only in the presence of hypothyroidism. Patients with precocious puberty must be studied carefully to determine the presence of a tumor in the thymus, adrenal gland, ovary or pineal gland. If no tumor is present, treatment consists in intelligent guidance of the child. In addition, it may be advisable to stimulate growth with pituitary material, for children with this condition show rapid early growth, and then with maturity growth ceases and they eventually become dwarfs.

RAUH, Cincinnati.

PNEUMOCOCCIC SEPSIS AND PERITONITIS IN A CHILD SUFFERING FROM NEPHROSIS CURED WITH SULFAPYRIDINE. E. SCHIFF, Ann. pædiat. **157**:332, 1941.

The author reports the remarkable rapid cure with sulfapyridine of pneumococcic sepsis and peritonitis in a child suffering from lipid nephrosis. Reference is made to several exceptional features in the clinical course of the case.

AUTHOR'S SUMMARY.

ENURESIS. KARL HEYMANN, Ann. pædiat. **158**:166, 1942.

The control of the emission of urine is one of the particular examples of reflex inhibitions. The child learns this control in early infancy. These inhibitions have a strong affinity to rhythmic processes, so that they can be influenced by keeping strictly to certain hours. In this connection the small child learns through the punctuality of the person who trains it. All that the child possesses in the way of a rhythmic capacity of experience is widely claimed by this kind of training. But if this rhythmic capacity of experience is claimed too much in other directions, then the control of the emission of urine may fail. Jactitation and the shaking of difficult children rob the reflex inhibitions of their rhythmic components, so that these reflex inhibitions fail. The significance of a rhythmic experience in the control of the emission of urine is then shown in the case of a color-blind boy afflicted with enuresis. The incapacity of inserting intervals, which is in this case enhanced through color blindness, renders the control of the emission of urine impossible, for no rhythmic experience is possible without the experience of intervals.

AUTHOR'S SUMMARY.

Diseases of the Ductless Glands; Endocrinology

ENDOCRINE PROBLEMS IN ADOLESCENCE. EPHRAIM SHORR, J. Pediat. **19**:327 (Sept.) 1941.

Shorr advances the point of view that most of the endocrine problems of adolescence are expressions of physiologic variations which can be best handled by a sane program of physical and mental hygiene. A review of those conditions for which specific glandular therapy exists is presented and the treatment outlined. Among these conditions are: amenorrhea, dysmenorrhea and menorrhagia in girls and delayed puberty with hypogonadism with or without maldescent of the testes in boys. Disturbances of the thyroid apparatus during adolescence, such as simple goiter with or without thyroid insufficiency, hypothyroidism and exophthalmic goiter are discussed. A brief review of the treatment of diabetes mellitus, hirsutism and virilism is also included.

RAUH, Cincinnati.

Diseases of the Muscles, Bones, Joints and Lymph Glands

ACUTE HEMATOGENOUS OSTEOMYELITIS. HOWARD MAHORNER and ALFRED P. CRAIN JR., Ann. Surg. **115**:790 (May) 1942.

In this paper the details of the study of 66 patients with primary acute hematogenous osteomyelitis admitted to Charity Hospital, New Orleans, between 1937 and 1940 inclusive are given and compared with observations in a previous study of 112 patients at the same institutions from 1930 to 1936 inclusive. In the present group the mortality was 6.6 per cent, while in the previous group it was 24 per cent. The paper discloses variations in the treatment which were responsible for the improvement in mortality.

It is shown that Negro children have the disease less frequently than white children and that males are more often affected than females. The disease is predominantly one of growing years. The mean age in both series was 9 years.

Among the important features responsible for the higher mortality were: unjustified emergency operation before the patient had been properly prepared

and failure to reestablish a normal physiologic state by fluid and electrolyte replacement and blood transfusion before operations were undertaken.

Chemotherapeutic measures and immunotherapy have added additional favorable influence in the therapy. Venous ligation in cases in which there are continuous positive blood cultures and immobilization by plaster cast are stressed by the authors.

BANTIN, Omaha.

CALCIUM AND PHOSPHORUS METABOLISM IN OSTEOMALACIA: XI. THE PATHOGENETIC ROLE OF PREGNANCY AND RELATIVE IMPORTANCE OF CALCIUM AND VITAMIN D SUPPLY. S. H. LIU, H. I. CHU, H. C. HSU, H. C. CHAO and S. H. CHEN, J. Clin. Investigation **20**:255 (May) 1941.

Data on calcium, phosphorus and nitrogen metabolism during the latter part of pregnancy were obtained on 10 subjects showing various states of skeletal storage of minerals and vitamin D nutrition. Given an adequate supply of vitamin D and calcium, patients with osteomalacia showed no inherent inability to retain minerals during pregnancy as compared with those with no skeletal depletion. The added requirement during gestation, unlike that in lactation, did not seem to go beyond fetal needs. However, such needs had to be filled at the expense of the maternal tissue if the supply of vitamin D and minerals was inadequate. Under such circumstances, pregnancy plays an important pathogenic role in osteomalacia, inasmuch as it hastens the skeletal demineralization. While high intake of calcium tends to ameliorate the effects of vitamin D deficiency, the latter conserves calcium. Of the two, vitamin D is probably more important, provided a reasonable level of calcium intake is available. The calcium requirement during pregnancy is conditioned by the prior skeletal store, the previous dietary intake and the state of vitamin D nutrition.

GUEST, Cincinnati.

GLANDULAR CYSTS. ALEJANDRO CEBALLOS, GUILLERMO OBEID and LUIS HARRINGTON, Rev. méd. latino-am. **27**:1287 (Sept.) 1941.

Glandular cysts in the cervical region are of bronchial origin and may be involved in a tuberculous adenitis. The authors emphasize the importance of diagnostic puncture and of staining the material by the May-Grünwald-Giemsa method, which enables one to determine the presence of scaleless epithelial cells that are peculiar to these cysts. These cells are round or polygonal, 30 to 50 microns in diameter, and have a small nucleus of grumous chromatin. Surgical extirpation is indicated when the diagnosis is confirmed in this manner.

DWYER, Kansas City, Mo.

LACUNAR SKULL DUE TO PRESSURE. CORNELIA DE LANGE, Ann. pædiat. **158**:97, 1942.

A healthy breast-fed child, born after a normal delivery, at the age of 2 months showed an acute hydrocephalus. The patient was admitted to the hospital, where the diagnosis of pachymeningosis hydrohaemorrhagica was made. The treatment consisted of a series of punctures of the anterior fontanel. The circumference of the head steadily increased, and the child appeared to be hydrocephalic; the sutures of the cranium had a tendency to close rapidly. In consequence of one of the punctures a mild meningitis developed, caused by Staphylococcus epidermidis. After closing of the sutures several soft places in the cranium were felt. Death came at the age of 10 months.

The postmortem examination showed a great many lacunas in the cranium, elevated borders of the anterior fontanel, absence of the lambdoid suture, scarcely visible metopic, sagittal and temporal sutures, multiple corticodural adhesions, a hydrocephalus internus and an occlusive membrane in the caudal part of the aqueduct of Sylvius.

The explanation which the author offers is that in this cranium with partial stenosis (absence of the lambdoid suture) the tendency to synostosis in the other

bones was so excessive that they united in spite of the highly increased intracranial pressure. The sutures not yielding to that pressure caused softening of those parts of the bones which in the normal development of the skull are the latest to ossify. In a comparison of the cranium of the patient with that of a normal child of nearly the same age it could be seen that normally the ossification of the skull is not the same over the whole surface of the bones. Examining it in daylight artificial light proved that the lacunas in the patient's cranium were situated fairly in the same places which in the normal skull are likewise more or less transparent.

AUTHOR'S SUMMARY.

Diseases of the Eye

COLOBOMA OF THE OPTIC NERVE IN THE HUMAN EMBRYO. B. F. PAYNE, Am. J. Ophth. **24**:386 (April) 1941.

Payne gives the following summary:

"1. An overgrowth of the retinal elements in a 61-mm. human embryo resulted in the inclusion of a fold of the retina in the optic nerve on the temporal side.

"2. The pigment epithelium was not included in the fold.

"3. Glial and mesodermal tissue replaced normal nerve markings on the temporal side, with disorganization of the columns of nuclei.

"4. From the histologic picture it is assumed that central vision would have been lost because of an interference with the papillomacular bundle had the embryo developed to maturity."

W. S. REESE [ARCH. OPHTH.].

CONGENITAL ANNULAR CATARACT. J. MALBRÁN and B. TOSI, Arch. de oftal. de Buenos Aires **15**:543 (Nov.) 1940.

Few cases of congenital annular cataract have been reported, the first reports having been mere presentations of anatomic observations and the others, with the exception of that of Hess, clinical reports. The literature is reviewed in detail and a case reported with clinical, slit lamp and microscopic (postoperative) details. Malbrán inclines in part to von Szily's views in considering the lesion a central cataract due to an idiokinetic disturbance and in part to the views of Collins, which attribute the lesion to interruption in the second stage of the development of the lens, with resulting nonformation of a central nucleus leading to a central membranous formation produced by apposition of the anterior and the posterior lens capsule and separating two peripheral lenticular masses which develop in a more or less disorderly fashion.

C. E. FINLAY [ARCH. OPHTH.].

OPHTHALMIC CHANGES IN CYSTINE DISEASE. E. BÜRKI, Ann. pædiat. **156**:324, 1941.

In a case of renal dwarfism in a boy 7 years old, many crystalline deposits were found in the cornea and conjunctiva. On microscopic examination, crystals were detected in the uvea as well as in the episclera, and rarely in the sclera. The crystals were cystine.

There are no reports in the literature of deposits of cystine in the eye. Examination of the eyes by the slit lamp will be important in the future in cases of renal dwarfism.

FROM THE AUTHOR'S SUMMARY.

ALLERGY STUDIES ON TUBERCULOUS EYES. B. BOROS, Arch. f. Ophth. **142**:356, 1940.

The author applies to ocular tuberculosis Gröer's concept of tuberculous allergy, according to which the intensity of local reactions to the application of allergens depends on the ratio of reactivity to susceptibility. The relative share of each of these two factors can be determined by the simultaneous application at different

places of two different concentrations of the stimulus, that is of tuberculin. If reactivity and susceptibility are in a state of equilibrium (called homodynamic allergy by Gröer) the product of the average diameter of the cutaneous reaction (read after twenty-four hours) times the negative logarithm of the tuberculin concentration is constant. If R_1 and R_2 were the average diameters of the cutaneous reactions produced by the concentrations of C_1 and C_2, respectively, of tuberculin in a case of homodynamic allergy, the proportion would hold:

$$R_1/R_2 = -\log C_2/-\log C_1, \text{ or } \frac{R_1 \times -\log C_1}{R_2 \times -\log C_2} = 1$$

If the latter ratio in a given case is greater than 1, that is if the increase in cutaneous reaction produced by a certain increase in tuberculin concentration is greater than in homodynamic allergy, Gröer spoke of pleoergic allergy, and in the opposite case, of pleoesthetic allergy. The interpretation of results of tuberculin tests in the light of Gröer's concept gives valuable clues with regard to the activity, healing tendency and probable future of tuberculous diseases occurring in children. In adults the allergic state of the skin may be different from that of other organs. (The experimental work of A. C. Woods and associates on regional differences in sensitivity to tuberculin is not mentioned.)

The three states of allergy were found to occur in patients with ocular tuberculous diseases as shown in the accompanying table.

States of Allergy in Ocular Tuberculous Diseases

	Number of Cases		
	Pleoergic	Homodynamic	Pleoesthetic
Phlyctenular keratitis	5	10	5
Iridocyclitis	8	4	1
Choroiditis	7	5	1
Sclerokeratitis	4	2	2
Retinal periphlebitis	2	2	1
Orbital periostitis	..	1	..

In the individual patient the allergic state was found not to vary with the different phases (activity, inactivity, progression, regression) of the ocular disease. A chemotherapeutic agent of the name rubrophen (trimethyldioxyoxytritan) seemed to modify the allergic state in the direction of less pleoergism or of greater pleoesthesia. Such alterations in the allergic state seemed to have a beneficial effect on the ocular disease. "In the pleoesthetic state tuberculin must not be used."

P. C. KRONFELD [ARCH. OPHTH.].

CORNEOSCLERAL CYST. M. VROLIJK, Acta ophth. **19**:44, 1941.

A congenital epithelial cyst at the limbus corneae in a girl of 10 is described. Theories as to the origin of such cysts are discussed.

O. P. PERKINS [ARCH. OPHTH.].

Skin Diseases; Allergy

HEREDITARY LYMPHEDEMA (NONNE-MILROY-MEIGE): REPORT OF A FAMILY WITH HEREDITARY LYMPHEDEMA ASSOCIATED WITH PTOSIS OF THE EYELID IN SEVERAL GENERATIONS. D. BLOOM, New York State J. Med. **41**:856, 1941.

Bloom has studied a family of 37 members in four generations showing a unique association of lymphedema of the lower extremities and ptosis of one or both eyelids. Six members had the lymphedema and the ptosis and 3 the ptosis only.

The author discusses the occurrence of inflammatory attacks, the association with spina bifida occulta, the presence of mental deficiency and the genetic mechanism of the disorder.

RONCHESE, Providence, R. I. [ARCH. DERMAT. & SYPH.].

ALLERGIC REACTIONS IN THE ABDOMEN. T. WOOD CLARKE, New York State J. Med. **41**:1642 (Aug. 15) 1941.

Allergic reactions in the abdomen may manifest themselves in four ways: hyperemia, edema, glandular hypersecretion and contraction of smooth muscles. Vomiting, severe abdominal cramps and collapse may occur in children. If allergy is not considered, mistakes in diagnosis may occur and result in unnecessary operative procedures. If the pain is associated with urticaria, hay fever or asthma, allergy must be suspected and a cutaneous test may be done.

AIKMAN, Rochester, N. Y.

ROENTGEN THERAPY OF HEMANGIOMATA. FRED M. HODGES, L. O. SNEAD and R. A. BERGER, Radiology **36**:700 (June) 1941.

The authors report on the treatment of 19 infants with angioma by means of contact roentgen therapy. The results were uniformly good. In three seconds 400 r measured in air was delivered to the affected areas every four to six weeks. In the discussion one of the authors agreed that if the dose is reduced to 200 r, there is less likelihood of telangiectasia. In some cases the rays were filtered. This method is rapid, safe and efficacious.

ABSTRACTER'S NOTE.—Radium plaques will probably be used less in the future by dermatologists and others, especially since shock-proof apparatus can be used close to the skin with no danger to the patient or to the parent or assistant holding the infant. Also a large dose can be delivered in a few seconds.

CIPOLLARO, New York [ARCH. DERMAT. & SYPH.].

ENDOCRINE FACTORS IN ACNE VULGARIS. E. LIPMAN COHEN, Brit. J. Dermat. **53**:231 (Aug.-Sept.); 269 (Oct.) 1941.

In two articles the author has given an exhaustive survey of the role that the endocrine glands have played in regard to causation and treatment of acne vulgaris. The strongest arguments in favor of an endocrine causation are the regularity of the appearance of the disorder at puberty and its variation with the menses. Acne occurs with abnormal frequency in conjunction with certain diseases of the endocrine system, such as tumors of the adrenal cortex and arrhenoblastomas, and also during the administration of androgens, such as testosterone propionate. Apart from these, it does not occur regularly with the major endocrine disorders. Particular confusion exists with regard to the results of treatment. It appears that in those cases in which some disease of the endocrine system is clearly present the treatment of that disease will also improve the acne; beyond that it is as yet impossible to draw final conclusions.

BLUEFARB, Chicago [ARCH. DERMAT. & SYPH.].

PRELIMINARY REPORT ON THE TREATMENT OF SCABIES WITH BENZYL BENZOATE. LUIS NÁJERA ANGULO and BERNABÉ JIMÉNEZ ROLDÁN, Rev. méd. latinoam. **26**:793 (April) 1941.

A single application of benzyl benzoate lotion cured 52 patients suffering from scabies, and two applications cured 28 patients. There were no failures. The authors found the treatment well tolerated even by women and children, without the production of dermatitis or secondary eczematizations. Complicated scabies was not aggravated; in fact, it was most often favorably influenced. It was not necessary for the patient to change his clothing, and only a preliminary cleansing hot bath was used.

LEIFER, New York [ARCH. DERMAT. & SYPH.].

A Characteristic Case of Ichthyosis Congenita Beginning as Lamellous Exfoliation and Without Malformations. Charlotte Trefzer, Ann. pædiat. **158**:120, 1942.

The author describes a case of congenital cutaneous changes, in which at the beginning the condition in no way differed from exfoliatio lamellosa but in which there developed in the fifth month of life a typical ichthyotic stage. Ichthyosis congenita was diagnosed, although the generally accepted demand that it be accompanied by malformations was not fulfilled. There was no consanguinity in the parents. No analogous case could be found in the literature; hence the further development of the symptom complex here described is of special interest.

Author's Summary.

Molluscum Contagiosum Corneae. R. Sysi, Acta ophth. **19**:25, 1941.

A 3 year old child presented the typical nodular lesions of molluscum contagiosum on the skin of the cheek, forehead and upper lip and on the border of the left upper eyelid.

The left eye showed a slight pericorneal injection and a central area of corneal infiltration about 4 mm. in diameter. In the midst of this infiltration was an elevated nodule about 1.5 mm. in diameter with an umbilicated center. This was excised, together with the nodule on the eyelid. The nodule from the skin showed the typical picture of molluscum contagiosum; that from the cornea showed pigmented corneal cells suggestive of cells of molluscum contagiosum, but the small size of the specimen made a satisfactory histologic examination impossible.

O. P. Perkins [Arch. Ophth.].

Surgery and Orthopedics

A Biochemical Investigation of the Tannic Acid and Sulfanilamide Treatment of Burns. J. de Vidas and A. C. McEachern, M. J. Australia **2**:470 (Oct. 25) 1941.

From an investigation of 16 patients ranging in age from 9 months to 10 years the authors conclude: 1. Sulfanilamide (7.5 per cent) in tannic acid (4 per cent) jelly has coagulum-forming properties similar to those of tannic acid jelly. 2. Absorption of sulfanilamide continues for thirty hours, quickly rising to a maximum level, of 5 mg. per hundred cubic centimeters, in the blood in eight or nine hours. 3. When burns are treated with sulfanilamide (7.5 per cent) and cod liver oil (25 per cent) in petrolatum, there is no comparable absorption of sulfanilamide. Tannic acid and sulfanilamide jelly produced satisfactory clinical results, but whether they were better than those obtained with tannic acid alone could not be decided from such a small number of cases.

Gonce Jr., Madison, Wis.

Miscellaneous

Generalized Muscular Weakness as a Toxic Reaction to Digitalis. John S. La Due, Proc. Soc. Exper. Biol. & Med. **48**:5 (Oct.) 1941.

The author reports his observations of prolonged use of digitalis for a 23 year old woman in whom extreme weakness was the outstanding complaint. When the administration of the drug was discontinued, strength returned. Four dogs given a crystalline cardiac glucoside also became extremely weak, as shown by tests with a treadmill. Strength returned promptly when the administration of the drug was discontinued.

Hansen, Minneapolis.

THE PEDIATRICIAN AND INTELLECTUAL CULTURE. WALTER PIAGGIO GARZÓN, Bol. Inst. internac. am. de protec. a la infancia **15**:223 (Oct.) 1941.

1. The pediatrician should try to attain a deep and vast culture, maintain his ideological values and unite his technical training with cultural instruction.

2. Higher culture (literature, philosophy) acts as exercise for the mind, helps to develop certain qualities or natural gifts (wise judgment, eagerness for observation, clinical flair, methodical reflection) and exercises a final influence on the tendency of one's ideas.

3. To maintain his spiritual position the pediatrician should apply himself to classical humanities. Reading, as an intellectual stimulant, should accompany psychologc activities.

4. An essential part of life should be devoted to impartial scientific investigation and to developing a vast culture of the soul.

5. The faculties of universities should be chosen among the most qualified doctors and those having the greatest cultural attainments.

6. It is of imperative necessity to intensify culture in the medical environment, by means of libraries, laboratories and centers for investigation and study.

7. The cultural level of the studious youth, and in particular that of the future physician, ought to be raised.

8. Intellectual production should depend on education.

9. Intellectual culture increases the hierarchy of the pediatrician and makes him more fit for his noble mission. FROM THE AUTHOR'S SUMMARY.

Book Reviews

Changes in the Knee Joint at Various Ages. By Granville A. Bennett, M.D., Hans Waine, M.D. and Walter Bauer, M.D. Price, $2.50. Pp. 162, with 9 illustrations and 31 plates. New York: The Commonwealth Fund, 1942.

This monograph is a terse, scholarly attempt to explain the nature and development of degenerative joint disease. The work was started in 1930 at the Harvard Medical School and the Massachusetts General Hospital in connection with the Robert W. Lovett Memorial Association, with the aim of gathering information concerning the anatomy and physiology of articulations and the nature of the diseases disturbing them. In addition, not only were detailed clinical studies of arthritic patients made from the important standpoint of pathology, but bacteriologic, metabolic and neuropathologic observations were included.

Knee joints were obtained post mortem or after amputation from patients ranging in age from 1 month to 90 years who, so far as was known, had no history or clinical evidence of articular disease. The joints were first examined roentgenologically; then they were opened for both macroscopic and microscopic examination. It was thus revealed that all the joints obtained from persons beyond the second decade of life exhibited alterations similar to those obtained in so-called degenerative joint disease or hypertrophic arthritis. The material studied permitted the establishment of a norm for each decade through life. A description of the development of degenerative joint disease combined with a review of the literature provided a basis for the discussion of the nature and cause of this common condition.

Pediatricians may be astonished to find the early stages at which the disease is started and will welcome this authoritative information so well based and recorded by text and illustrations. This work will be invaluable in an understanding of the pathogenesis and abnormal physiology of degenerative joint disease.

Heredity, Food and Environment in the Nutrition of Infants and Children. By George Dow Scott, M.D. Price, $5. Pp. 778, with no illustrations. Boston: Chapman & Grimes, Inc., 1942.

This book is a rhetorical Cook's tour of a large variety of subjects intimately and remotely related to nutrition. The reviewer shares the conviction of the author that it is important to consider adequately the biologic forces which condition the success or failure of a nutritional program, and he respects the author's painstaking attempt to provide those facts. He doubts, however, whether the reader's interest will survive this encyclopedic presentation. The author's aim is excellent, but he has wrecked his target with too much ammunition. In the first few chapters, on heredity and environment, the information presented is practically an epitomized version of a text on that subject. It is also doubtful whether details on disease processes and diagnosis contribute to the purpose of the book. The material on nutrition and metabolism is excellent, but some of it is far too detailed for the lay reader. The remainder of the book is a potpourri of applied psychology, physiology and physical therapy. It is almost impossible in a limited space to review the subject material considered by the author. The book would have genuine merit if it discussed in general the effect of heredity and environment on nutrition and if the chapters on disease and metabolism were condensed. The well documented bibliography at the end of each chapter would have permitted this. The chapters on "Physical and Psychic Stimuli" and "Nature's Appetizers" are well done but are speculative and hypothetic. As the book now stands it is far from a guide to child nutrition but is in reality a veritable maze.

Nutrition and Chemical Growth in Childhood: Volume I. Evaluation. By Icie G. Macy, Ph.D. Price, $5. Pp. 436, with 80 illustrations and 151 tables. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

This first volume of Dr. Macy's study on "Nutrition and Chemical Growth in Childhood" reports the methods of study and the results of an investigation of 29 healthy children over a period of ten years. The second volume, yet to be published, will be one of interpretation. These children lived in groups of 9 to 12 in the Methodist Village in Michigan. It was thus possible to have thoroughly controlled feeding conditions and fairly similar environmental factors. A definite attempt was made both to satisfy the children in regard to appetite and to meet the requirements for metabolic studies with as little interference with their normal activities as possible.

Numerous studies of the physiologic and chemical aspects of digestion and excretion are presented. Energy metabolism is studied in relation to fat, carbohydrate and protein and to requirements for growth.

Balance studies on nitrogen, calcium, magnesium, sodium, potassium, sulfur, chlorine, phosphorus, copper, zinc, iron, nickel, manganese and carbon have been made. There is also a chapter on various chemical elements in the blood showing the partition between plasma and cells. This promises to be a fruitful field of study, as the blood cells may be taken as fairly representative of other tissue cells.

The methods are given in detail and form a valuable portion of such a book, which will probably be used largely for reference. The index is thoroughly satisfactory.

Sulfanilamide and Related Compounds in General Practice. By Wesley W. Spink. Price, $3. Pp. 374. Chicago: The Year Book Publishers, Inc., 1942.

Few books on medical subjects at any time have ever approximated the excellence of this publication, now in its second edition, on this timely and most important subject. The author reveals a background of extensive study and clinical experience, rare in variety and scope in the use of these new drugs in the practice of clinical medicine in its varied fields. To students, teachers and practitioners this volume will appeal with great and equal interest, for the purely academic phases as well as the practical application of these remedies are succinctly presented in pleasing and attractive form. The discovery, history and application of this new form of therapy to the treatment of human disease are well presented. The whole volume is so complete that the author seems to have anticipated almost any inquiry on the subject of these compounds. The newest and latest medical fields to which these compounds have been applied are also completely presented. The limitations and dangers as well as the possibilities of this form of therapy are clearly indicated, and the book will supply a reliable guide for any one in the varied uses of these new remedies. It is a distinct contribution to every field of medical practice and will make a valuable addition to any medical library.

Bonnie's Baby Brother and How He Grew. By Elizabeth Rider Montgomery. Price, $2. Pp. 95, with 46 illustrations. Philadelphia and New York: Frederick A. Stokes Company, 1942.

This is a delightful book telling in story form and pictures how a little girl of almost 5 years watched her baby brother grow and develop during the first year of his life. Such a book given or read and reread to a small child would do much to give him happiness and understanding in his relationship to a new baby. It meets a long felt need and may be recommended wholeheartedly. The excellent photographic illustrations are by Ralph W. Berry.